AstraZeneca

Statistical Analysis Plan

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A randomized clinical study to assess the impact of Symbicort® pMDI medication reminders on adherence in COPD patients

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A randomized clinical study to assess the impact of Symbicort® pMDI medication reminders on adherence in COPD patients

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List of Abbreviations

Abbreviation or Special Term	Explanation
AE	Adverse Event
ANCOVA	Analysis of covariance
AZDD	AstraZeneca Drug Dictionary
CCQ	Clinical COPD Questionnaire
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
EOT	End of Treatment
FAS	Full Analysis Set
FEV_1	Forced Expiratory Volume
FVC	Forced Vital Capacity
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
MCID	Minimal Clinically Important Difference
PT	Preferred Term
pMDI	Pressurized Metered-Dose Inhaler
PP	Per-Protocol Analysis Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class

Amendment History

Date	Version	Brief Description of Change
15 June 2017	V1.0	N/A

Purpose of this SAP

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the final analysis of data collected for protocol/study number D589CL00003, "A randomized clinical study to assess the impact of Symbicort® pMDI medication reminders on adherence in COPD patients" currently under protocol version 3.0, dated 03 October 2016, and version 2 electronic case report forms (CRF), dated 26 July 2016.

Detailed technical specifications regarding derived analysis datasets and programming will be included in separate documents. Results of the planned analyses described in this SAP will be included in a streamlined Clinical Study Report.

1. Study Design

This is a 26-week, 2-arm, randomized, multicenter, phase IV study to evaluate the impact of medication reminders on adherence to Symbicort pressurized metered-dose inhaler (pMDI), budesonide/formoterol, 160/4.5 µg x 2 actuations twice daily (bid) in subjects with chronic obstructive pulmonary disease (COPD). Approximately six study sites within the United States will enroll approximately 487 subjects in order to randomize a total of 414 adult subjects with COPD (e.g., 15% dropout rate).

1.1 Sample Size Justification

The sample size is based on the primary endpoint of an 18% absolute increase in mean number of daily sets of Symbicort puffs in COPD subjects receiving reminders compared with those who are not receiving reminders. The null hypothesis is that there is no difference in adherence to Symbicort as measured by sets of puffs/day in COPD subjects who receive reminders compared with those who do not receive reminders. The alternate hypothesis is that there is a difference in adherence to Symbicort as measured by sets of puffs/day in COPD subjects who receive reminders compared with those who do not receive reminders. A mean of two sets of two Symbicort puffs per day is defined as 100% adherence to Symbicort. Based on the information received from the Health Core Research Environment claims database, and the Simmons et al 1996 manuscript from the Lung Health Study, the mean Symbicort sets of puffs per day is assumed to be 1.0 (50% adherence) in COPD subjects. It is assumed that the mean Symbicort sets of puffs per day in subjects receiving reminders will be 1.18 which is an improvement in adherence of 18 percentage points compared with subjects not receiving reminders. Thus a total sample size of 352 achieve ~ 80% power to reject null hypothesis of equal means of daily sets of Symbicort puffs per day when mean difference is $\mu 1 - \mu 2 = 0.18$ with a standard deviation for both groups of 0.6 and with a significance level（α） of 0.05 using a two-sided two sample equal-variance t-test. A dropout rate of 15% will give rise to the total sample size of approximately 414 subjects. Therefore, the study will randomize approximately 207 subjects in each individual group. The sample size was calculated using PASS software.

1.2 Subject Randomization

Subjects who met all eligibility criteria will be randomized with a 1:1 allocation ratio to either an intervention group or a control group. A randomization schedule consisting of 250 blocks with a block size of four was created and implemented by a third party vendor.

2. Objectives

2.1 Primary Objective

The primary objective of this study is to demonstrate the impact of the BreatheMate medication reminders on adherence to Symbicort in COPD patients.

2.2 Secondary Objectives

The secondary objectives of this study are to:

- Demonstrate improved symptom control from Baseline with use of medication reminders.
- Demonstrate the impact of the BreatheMate medication reminders on additional adherence measures.

3. Analysis Sets

3.1 Definition of Analysis Sets

Three analysis populations are defined: screened, full analysis set (FAS) and per-protocol analysis set (PP).

The screened population consists of all subjects who signed an informed consent document and were assigned an enrollment number, regardless of whether or not they met all eligibility criteria. The screened population also includes subjects who participated in the run-in period, regardless of whether or not they were assigned a randomization number. Study disposition will be summarized using the screened population.

The FAS population consists of screened subjects who were randomized and took at least one inhalation of Symbicort during the treatment phase of the study. All study endpoints will be analyzed using the FAS population.

The PP population consists of FAS subjects who have met all eligibility criteria, had no major protocol deviations and had a minimum of 60 days of device time on study (defined in Section 4.4.5). All primary and secondary endpoints will also be analyzed using the PP population.

4. Outcomes

The primary, secondary and safety outcomes of this study are described in the following section. Details regarding the analysis of each outcome is described in Section 5.

4.1 Primary Outcome: Average Number of Sets of Adherent Symbicort Puffs per Day Over the 26 Week Treatment Period

The primary outcome for this study is the average number of sets of adherent Symbicort puffs per day for each group, over an average of 26 weeks. Detailed information regarding the calculation of sets of Symbicort puffs per day can be found in Section 4.4.1.

4.2 Secondary Outcomes: Additional Adherence Measures

The secondary outcomes for this study consist of indicators of improved symptom control from baseline and additional adherence measures: device time on study, number of Symbicort inhalations per day, number of complete sets of Symbicort puffs, Clinical COPD Questionnaire (CCQ) total and domain scores at Baseline, end of treatment (EOT) and change over the six month treatment period, CCQ scores (intervention group only) for each two month study interval, the number of sets of puffs per day, number of double puffs, number of adherent days, number of no use days, number of underuse days, number of overuse days, number of overuse alert days and number of Symbicort prescription fills.

4.2.1 Device Time on Study

Device time on study is the amount of time, in days, a subject is in the treatment phase of the study with a device that is actively capturing data, even if the device is not syncing to the Adherium network. Detailed information regarding the calculation of device time on study can be found in Section 4.4.5.

4.2.2 Average Number of Symbicort Inhalations per Day

Symbicort inhalations is the total number of singular puffs of Symbicort, regardless of the timing of those puffs, a subject takes per day. Symbicort inhalations per day will be determined only for the days during device time on study.

4.2.3 Average Number of Complete Sets of Symbicort Puffs per Day

A complete set of Symbicort puffs is two Symbicort puffs that are taken within 60 minutes of each other, on the same calendar day (i.e. January 1 from 12:00:00 AM to 11:59:59 PM). The mean number of complete sets of Symbicort puffs per day will be computed for each subject, for each of the three two-month study intervals and for the whole 26 week study period. Complete sets of Symbicort puffs per day will be determined only for the days during device time on study. Detailed information regarding the calculation of complete sets of Symbicort puffs per day can be found in Section 4.4.2.

4.2.4 Clinical COPD Questionnaire Scores

The CCQ is used to measure a subject's COPD symptom control. Clinical COPD Questionnaire data will be collected for all subjects at Baseline and EOT visits, and the change in CCQ total and domain scores for the entire study will be computed for each group by:

$Change\ in\ X_{Baseline\ to\ EOT} = X\ Score_{EOT} - X\ Score_{Baseline}$, where *X* is the CCQ total score and domain (symptom, mental, function) scores.

In addition, subjects in the intervention group take the CCQ weekly (whereas the control group only takes the CCQ at Baseline and EOT) to determine if the medication reminders have any impact on subjects' symptom control throughout the study.

The entire 26 week treatment period will be broken down into three, two-month intervals:

- Interval 1: From study day 1 to study day 63 (inclusive)
- Interval 2: Study day 64 to study day 126 (inclusive)
- Interval 3: Study day 127 to EOT (inclusive)

The last week of each two-month interval is used to represent that two-month interval and the change in CCQ scores between each of the three two-month intervals will be summarized using the following formulas:

- $Change\ in\ X_{Interval\ 2\ to\ Interval\ 1} = X\ Score_{Week\ 18} - X\ Score_{Week\ 9}$
- $Change\ in\ X_{Interval\ 3\ to\ Interval\ 2} = X\ Score_{EOT} - X\ Score_{Week\ 18}$
- $Change\ in\ X_{Interval\ 3\ to\ Interval\ 1} = X\ Score_{EOT} - X\ Score_{Week\ 9}$

Where *X* is the CCQ total and each of the three domain scores (e.g., 12 change scores for the intervention group and four change scores for the control group).

4.2.5 Average Number of Sets of Adherent Symbicort Puffs per Day During Each Two Month Interval

The mean number of adherent sets of Symbicort puffs per day will be computed for each subject, for each of the three two-month study intervals. Sets of Symbicort puffs per day will be determined only for the days during device time on study.

4.2.6 Number of Double Puffs

A double puff occurs when the inhaler is depressed twice, in quick secession, and both puffs are inhaled in one breath. A set of puffs is considered a double puff if two puffs are taken within one second of each other. Descriptive statistics on double puffs will be summarized and presented for the days during device time on study.

4.2.7 Number of Adherent Days

Adherent days is the number of treatment days a subject takes two sets of two puffs of Symbicort and each inhalation in a puff set is within 60 minutes of each other. Treatment days refers to the number of days of device time on study. Adherent days will be calculated only up until the day a subject withdraws from or completes the study. Detailed information regarding the calculation of adherent days is presented in Section 4.4.1.

4.2.8 Number of No Use Days

No use days is the number of treatment days a subject takes zero inhalations of Symbicort during device time on study. No use days will be calculated up to the day before the subject withdraws from or completes the study.

4.2.9 Number of Underuse Days

Underuse days is the number of treatment days a subject takes between one and three (inclusive) inhalations of Symbicort during device time on study. Underuse days will be calculated up to the day before the subject withdraws from or completes the study.

4.2.10 Number of Overuse Days

Overuse days is the number of treatment days a subject takes between five and ten (inclusive) inhalations of Symbicort during device time on study. Overuse days will be calculated up to the day before the subject withdraws from or completes the study.

4.2.11 Number of Overuse Alert Days

Overuse alert days is the number of treatment days a subject takes 11 or more inhalations of Symbicort during device time on study. Overuse alert days will be calculated up to the day before the subject withdraws from or completes the study.

4.2.12 Number of Symbicort Prescription Fills

Prescription fills is the number of Symbicort prescriptions a subject fills at their pharmacy during the 26-week treatment period. Consideration of whether or not a subject filled their prescription occurs during device time on study with the expectation that for each 30.25 days of device time on study a subject will have one Symbicort prescription fill. The expected total number of Symbicort prescription fills will be reduced by one for those subjects who were given a supply of Symbicort at randomization.

4.3 Safety Outcome

The safety outcomes for this study is concomitant medication use and adverse events. Concomitant medications are considered to be all medication taken at the time of study entry (e.g., study day 1) through Day 210 of the study (30 days after Visit 3 which occurs on Day 180 (EOT visit)), irrespective of the subject's device time on study.

A summary table of all treatment-emergent serious adverse events (SAEs) and AEs leading to treatment discontinuation; whether there is a reasonable possibility AE was cause by Symbicort; and patients who withdraw from the study due to an AE will be analyzed as categorical variables. AEs that occur within 30 days of EOT will be considered as treatment emergent. Data will be summarized by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or higher.

A summary of Symbicort usage during device study time will also be presented as a safety outcome. Symbicort usage will be summarized by the number of Symbicort puffs per day subjects take during device time on study. Symbicort usage will be determined up to the day before the subject withdraws from the study or the day before the EOT.

4.4 Definitions

The following section describes concepts and terms that are associated with the primary and secondary outcomes, and provides more robust information of their derivation.

4.4.1 Symbicort Adherence:

Adherent Symbicort puffs are defined as a subject taking a dosing regimen of exactly two sets of two Symbicort puffs per day, four puffs total, throughout the 26 week treatment period. Subjects who do not take exactly two sets of two puffs on any given day throughout their device time on study (defined in Section 4.4.5) will be considered non-adherent for that day. For subjects who take more than two sets of Symbicort puffs on any given day will be considered non-adherent. For example, if a subject has six puffs, each set of two puffs taken within 60 minutes of each other for a total of three puff sets, the subject would be considered non-adherent, and assigned a value of '0' for that day. On any given day, for subjects who have four puffs, where each set of two puffs is taken within 60 minutes of each other, for a total of two puff sets, the subject would be considered adherent and assigned a value of '2' for that day.

In this study, a day is defined as one calendar day (i.e. January 1 from 12:00:00 AM to 11:59:59 PM). To qualify as a "set", two puffs must be taken on the same day, within 60 minutes of each other. There is no minimum amount of time needed between puffs to qualify as a set for a given day. There is also no minimum amount of time needed between the two sets of puffs.

Subjects who do not take exactly four puffs of Symbicort on any given day, the first and second puffs taken within 60 minutes of each other and the third and fourth puffs taken within 60 minutes of each other puffs, will be assigned a value of '0' for that day, regardless of the timing between puffs taken. For subjects who take exactly four puffs on any given day, time between puffs will be calculated as follows in order to determine if two puffs contribute to a set on a given day *i*:

$$Set\ 1_{\ day\ i} = \left(LOG\_DATE\ A\ \&\ TIME_{\ Puff\ 2} - LOG\_DATE\ A\ \ \&\ TIME_{Puff\ 1}\right) \leq 60\ mins$$

$$Set\ 2_{\ day\ i} = \left(LOG\_DATE\ A\ \&\ TIME_{\ Puff\ 4} - LOG\_DATE\ A\ \ \&\ TIME_{Puff\ 3}\right) \leq 60\ mins$$

where LOG_DATE A & TIME is the vendor Adherium collected data.

A subject's adherence on a given day *i*, where *i* = 2 to the day before end of treatment (EOT, date of final phone/device returned), is defined by

$$Adherent_{day_i} = 2 \; if \; only \; Set \; 1_{day \; i} \; and \; Set \; 2_{day \; i} \; both \; occurred, otherwise \; equal \; to \; 0.$$

To determine a subject's total number of adherent days:

$$Adherent \; Days \; for \; a \; given \; subject = \sum_{i=2}^{EOT-1} Adherent_{day_i}$$

This algorithm starts on Study Day 2 since it is highly unlikely that all subjects will have taken four inhalations on the date of device and phone are dispensed (Baseline). In order for four inhalations to occur, all subjects would need to have received the BreatheMate device in the morning prior to when subjects normally take their first dose. This algorithm also ends one day prior to subjects' EOT since on EOT the subject will return the BreatheMate device, and it is highly unlikely that all subjects will have taken all four inhalations prior to returning the BreatheMate device.

A sensitivity analysis to the average number of sets of adherent Symbicort puffs per day over the 26 Week treatment period will be performed. This analysis will involve a multivariable logistic regression model to determine predictors of adherence. Subjects who had a proportion of adherent days of at least 80% during device time on study are considered adherent for this analysis. Details regarding the sensitivity analysis are described in Section 5.3.1.2.

4.4.2 Complete Sets of Symbicort Puffs

To qualify as a "complete set", two puffs must be taken on the same calendar day, within 60 minutes of each other. On any given day, there is no minimum amount of time needed between puffs to qualify as a set, no minimum amount of time needed between sets of puffs and no maximum amount of sets that can be taken (i.e. no capping). Time between puffs will be calculated as follows in order to determine if two puffs (*k*) contribute to a set *i* on day *j*:

$$Set \; i_{\; day \; j} = \left(LOG\_DATE \; A \; \& \; TIME_{\; Puff \; k+1} - LOG\_DATE \; A \; \& \; TIME_{Puff \; k}\right) \leq 60 \; mins$$

where *i* is the index for the number of sets of puffs, *j* is the index for the number of device time on study days and *k* is the index number for number of puffs (*k* = 1 to *K*) on the j^{th} day.

If the time between two consecutive puffs is not within 60 minutes of each other, then the timing of puff *k*+1 and puff *k*+2 is examined:

$$Set \; i_{\; day \; j} = \left(LOG\_DATE \; A \; \& \; TIME_{Puff \; k+2} - LOG\_DATE \; A \; \& \; TIME_{Puff \; k+1}\right) \leq 60 \; mins,$$

where LOG_DATE A & TIME is obtained through Adherium, vendor collected data.

For every two puffs, for a given subject on a given device time on study day, that meet the criteria for a complete set of puffs, the subject will be assigned a value of '1' for each complete puff set. For example, if a subject has three complete sets of puffs for one day; meaning six inhalations, with each pair being within 60 minutes apart, then that subject will be assigned a value of '3' (as 1+1+1=3) for that day. Additionally, when computing subjects' complete sets of puffs, fractional sets will not be taken into consideration. As an example, if a subject has five puffs in one day, with two pairs of two inhalations occuring within 60 minutes and one additional inhalation, then the unpaired inhalation will not be counted as a half a puff set and the subject will be assigned a value of 1+1='2' for that day.

4.4.3 Baseline:

For all outcomes other than those associated with Symbicort usage, Baseline is defined as the date randomization occurred. For subjects who are not already using Symbicort at study entry, baseline assessments may span the 28 days prior to and including the randomization date. If multiple Baseline observations for a given assessment exist, the assessment on the randomization date is used. If an assessment on the date of randomization is not available, the assessment closest to the randomization date is used for the analysis. Baseline is considered study day '1'.

For outcomes derived from Symbicort inhalation data, Baseline is defined as the date the initial phone and device were dispensed.

4.4.4 End of Study:

End of study is defined as the date captured on the Follow-up Telephone Contact eCRF or the date of withdrawal if a subject withdrew from the study.

4.4.5 Device Time on Study:

Device time on study is defined as one of the following:

(i) For instances where the subject only received one phone/BreatheMate device and the device was capturing Symbicort usage data regardless of syncing capabilities to the Adherium network device time on study is defined as the duration between the date the device and phone was dispensed and returned [Phone eCRF: PHONEDISDAT and PHONERTNDAT, respectively].
(PHONERTNDAT - PHONEDISDAT) - 1;

(ii) For instances where the subject received more than one phone/BreatheMate device and each device is capturing Symbicort usage data regardless of syncing capabilities to the Adherium network, device time on study is the sum of the days between the date each device and phone was dispensed and returned. Equation provided below is for the scenario of a subject receiving two BreatheMate devices).

Device Time $_{Device\ 1}$: (PHONERTNDAT$_{Device\ 1}$ – PHONEDISDAT$_{Device\ 1}$)

Device Time $_{Device\ 2}$: (PHONERTNDAT$_{Device\ 2}$ – PHONEDISDAT$_{Device\ 2}$)

Device Time on Study = Device Time $_{Device\ 1}$ + Device Time $_{Device\ 2}$

4.4.6 Clinical COPD Questionnaire:

The CCQ is a 10-item questionnaire (e.g., Q1-Q10) used to assess a subject's COPD symptom control. Each item ranges between never = 0 (a very good health status) to almost all the time = 6 (extremely poor health status) for Q1 through Q6, and not limited at all = 0 to totally limited/ unable to do = 6 for Q7 through Q10, and is equally weighted. The CCQ provides a Total Score and three domain scores: Symptom, Functional State and Mental State.

- CCQ Total Score derivation:

$$CCQ\ Total\ Score = \frac{((Symptom\ Domain\ Score) * 4 + (Functional\ State\ Domain\ Score) * 4 + (Mental\ State\ Domain\ Score) * 2}{10}$$

CCQ Total Score range: 0 – 6

CCQ Total Score meaning: A higher score corresponds to a lower health status

- Symptom domain score derivation:

$$Symptom\ Domain\ score = \frac{Q1 + Q2 + Q5 + Q6}{Number\ of\ items\ answered}$$

Symptom domain score range: 0 – 6

Symptom domain score meaning: A higher score corresponds to a greater negative impact of COPD symptoms

- Functional State domain score derivation:

$$Functional\ State\ domain\ score = \frac{Q7 + Q8 + Q9 + Q10}{Number\ of\ items\ answered}$$

Functional State domain score range: 0 – 6

Functional State domain score meaning: A higher score corresponds to lower health function

- Mental State domain score derivation:

$$Mental\ State\ domain\ score = \frac{Q3 + Q4}{Number\ of\ items\ answered}$$

Mental State domain score range: 0 – 6

Mental State domain score meaning: A higher score corresponds to lower mental state

Rules for Handling Missing CCQ Data

The table below outlines the scoring rules for calculating the domain scores with missing data.

Missing Data Rules for Calculating CCQ Scores[1]

Domain	No. items in domain	No. items required	% required items
Symptom	4	3	75
Functional state	4	3	75
Mental state	2	2	100

[1]Clinical COPD Questionnaire website (http://ccq.nl/?page_id=15)

If missing data exists, the total CCQ score is only calculated if each of the three domain scores can be calculated. For example, if one item was missing in the Mental State domain, this domain cannot be computed (e.g., missing). Thus, the total CCQ score will also be missing.

The minimal clinically important difference (MCID) for the CCQ Total Score is a decrease of at least 0.4 units from the Baseline score (Kon et al., 2014). A 'MCID responder' is a subject who achieves a MCID from their Baseline to their EOT CCQ Total Score.

4.4.7 Subject Rescreen:

A rescreened subject is defined as a subject for whom the CRF question "Is the subject a rescreen subject for this protocol?" was answered "Yes".

4.4.8 COPD Severity Level Determined by Lung Function:

COPD severity level is categorized into the following two categories based on the subject's reported severity of COPD disease reported on the Pulmonary Exacerbation History eCRF:

- Moderate: post-bronchodilator FEV_1 % predicted 50 – 79%
- Severe/Very Severe: post-bronchodilator FEV_1 % predicted < 50%

4.4.9 COPD Exacerbation Risk at Baseline:

A subject's COPD exacerbation severity at Baseline will be classified into one of two categories, as follows:

- Not Severe: Subject experienced either (i) zero exacerbations within the past 12 months prior to Baseline or (ii) one exacerbation *not* requiring hospitalization within the past 12 months prior to Baseline.

- Severe: Subject experienced either (i) most recent exacerbation within the past 12 months prior to Baseline *required* hospitalization or (ii) at least two exacerbations, regardless of hospitalization, within the past 12 months prior to Baseline.

5. Analysis Methods

Statistical analysis and generation of all tables and listings will be performed using SAS® (SAS Institute, North Carolina), version 9.4 or higher.

5.1 General Principles

5.1.1 Rules for Reporting Statistics

Continuous variables will be presented as the number of non-missing observations, mean, standard deviation (SD), median, minimum, maximum (e.g., range) and number of missing observations. The same number of decimal places as in the raw data will be presented when reporting minimum and maximum, one more decimal place than in the raw data when reporting mean and median, and two more decimal places than in the raw data when reporting SD.

Categorical variables will be summarized as counts and percentage (%) of subjects in each category, unless otherwise specified. Counts of missing data will be provided in all tables for information only. Percentages will not include the missing category and are calculated over the number of subjects with available (non-missing) data. Percentages will be rounded to one decimal place.

All significance tests will be two-sided, and conducted at the 0.05 significance level, except for those involing the logistic regression model used to determine secondary outcome ANCOVA model covariates (more details in Section 5.3.1.2). A significance level of 0.25 for the univariate modeling and 0.15 for the multiple regressions will be used to determine which covariates should be retained from that model for all subgroup analyses.

5.1.2 Rules for Handling Missing Data

Missing data will not be imputed and conventions for missing CCQ responses are described in Section 4.4.6. Data will be analyzed and presented as they are recorded in the database with the exception of any observation that has a recorded “Date of Visit” that also has the “Not Done” box checked. These observations will not be included in the analysis since the EDC system does not allow sites to delete the date once entered. Sites are instructed per the eCRF Completion Guidelines to also check the “Not Done” field if the “Date of Visit” was entered in error. As a general rule, partially missing dates such as missing month and/or day will not be imputed since there is no planned analyses of any date fields that allow partial dates.

5.2 Descriptive Analysis

Each descriptive analysis described below will be summarized using the FAS population, by group and overall, with the exception of subject disposition which will be summarized using the screened population.

5.2.1 Subject Disposition

The number of subjects screened, rescreened, enrolled and randomized will be reported, by group and overall. The number and percentage of subjects who completed and discontinued the study will also be reported. Reasons for discontinuation include: death, device technology issues, development of study-specific withdrawal criteria, lost to follow up, physician decision, screen failure, subject decision, study terminated by sponsor and other. The number and percentage of subjects in the Full Analysis and Per-Protocol Analysis sets will also be reported.

Protocol deviations identified throughout the study will be summarized descriptively in a table for the FAS population. The type of protocol deviation (eligibility criteria, study conduct, technology issue, etc.) and severity (major, minor) of protocol deviation will be presented. All protocol deviations will be presented in a listing.

5.2.2 Subject Demographics

Demographics include age, sex, race, ethnicity, most recent relative to baseline post-bronchodilator FEV_1 and most recent relative to baseline post-bronchodilator FEV_1/Forced Vital Capacity (FVC) ratio. Age is calculated as an integer rounded down from birthdate to date of informed consent, using the equation below:

$$Age = \frac{((Date\ of\ Informed\ Consent - Birth\ Date) + 1)}{365.25}$$

In addition, demographic differences between the two treatment groups will be compared using a chi-square test for categorical characteristics, and continuous values will be compared using a t-test, when applicable. Demographic data will presented in a listing.

5.2.3 Vital Signs

Vital signs include seated pulse, seated systolic blood pressure, seated diastolic blood pressure, respiratory rate, temperature, height (Baseline only) and weight (Baseline only). Baseline vital signs will be summarized by visit (Baseline and EOT).

Vital sign data will be presented in a listing.

5.2.4 Physical Examination and Subject History

Physical examination and subject history summarization will include the number and percentage of subjects who had a (i) physical examination performed, (ii) relevant medical condition, (iii) relevant surgery and (iv) any significant findings.

Physical examination data will be presented in a listing.

5.2.5 Medical History

The number of subjects with and without a medical condition, and medical condition type will be summarized. The number and percentage of subjects with a given medical condition will be stratified by the subjects' medical condition status (e.g., on-going and resolved), and the medical condition medication status (e.g., currently taking medication for condition, not taking medication for condition).

Medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary, version 19.1. Coded medical condition terms will be summarized by MedDRA System Organ Class (SOC) and Preferred Term (PT). SOC terms will be sorted alphabetically and PTs will be sorted in order of descending frequency of the total column within each SOC. If a subject reports the same event (the same PT) multiple times, the subject will be counted only once.

Coded medical history terms will be presented in a listing.

5.2.6 COPD Exacerbation History

COPD exacerbation history includes number of COPD exacerbations within the last 12 months, whether a subject was hospitalized for any recent exacerbations and COPD medication type.

COPD exacerbation history will be presented in a listing.

5.2.7 Smoking History

Smoking history includes smoker status, number of packs/day, number of years cigarettes consumed and number of pack years.

Smoking history information will be presented in a listing.

5.2.8 BreatheMate User Satisfaction Survey

BreatheMate User Satisfaction Survey responses will be summarized descriptively with counts and percentages by question. Responses will be presented in a listing.

5.3 Primary Analysis

The primary analysis on the mean number of sets of adherent Symbicort puffs (defined in Section 4.4.1) per day over the 26 week treatment period will be based on the FAS and PP populations.

5.3.1 Number of Sets of Adherent Symbicort Puffs/Day over 26 Weeks

The mean number of sets of adherent Symbicort puffs/day throughout the 26 week treatment period will be summarized descriptively by group (control vs. intervention), and overall. The effect of medication reminders on Symbicort adherence will be evaluated using a t-test. The equality of variances will also be tested and in the case where variances are not equal, the Satterthwaite-t test will be reported.

5.3.1.1 Subgroup Analyses

The mean number of sets of adherent Symbicort puffs/day throughout the 26 week treatment period will also be summarized for the following sub-groups and the effect of medication reminders on the average Symbicort puffs/day will be also be evaluated using a t-test:

- Adherent vs. Non-adherent subjects: Categorized by whether or not a subject had a proportion of 80% or more adherent days during device time on study.
- Overdosed vs. Non-overdosed subjects: A subject is considered to have overdosed on Symbicort if on the Overdose CRF, the question "Any Symbicort overdoses?' is answered 'Yes' for any day during the study.

In addition to the subgroups described above, every covariate found to be significant from the logistic regression model (two-step approach, see Section 5.3.1.2 for more details) will then be evaluated by a t-test, stratified by group. For each t-test conducted, the equality of variances will be tested and in the case where variances are not equal, the Satterthwaite-t test will be reported.

If any continuous covariate (age, number of COPD exacerbations, and device time on study) is found to be significant by the logistic regression model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically relevant cut point based on the data available. The subgroup analysis will only be performed if there are at least five subjects within each subgroup.

5.3.1.2 Sensitivity Analysis

A sensitivity analysis to the primary outcome of average number of sets of adherent Symbicort puffs per day over the 26 week treatment period will be performed. A multivariable logistic regression model will be used to determine predictors of adherence. The dependent variable will be whether or not a subject had a proportion of adherent days of at least 80% during device time on study. A two-step process for identifying model covariates using a logistic regression where the dependent variable will be whether or not a subject had a proportion of adherent days of at least 80% during device time on study will be followed. First, univariate logistic regressions

using the covariates specified below will be performed using a significance threshold of 0.25 (Step 1). Then a subsequent multiple logistic regression, using only the covariates identified in Step 1 will be performed using a significance threshold of 0.15 (Step 2). Only covariates that then reach the 0.15 significance level from the multivariable logistic regression in Step 2 will be included in subsequent secondary outcome ANCOVA models.

A subject's proportion of adherent days will be calculated as follows:

$$Proportion\ of\ Adherent\ Days\ (P_{adh}) = \frac{Subject's\ Number\ of\ Adherent\ Days}{Subject's\ Device\ Time\ on\ Study\ (days)}$$

The model will be specified with a Binomial distribution and a logit link function:

$$\text{logit}(E(Y)) = \log\left(\frac{E(Y)}{1-E(Y)}\right) = \beta_0 + \cdots + \beta_p x_p$$

Where *E(Y) = 1 if* $P_{adh} \geq 0.80$*; otherwise E(Y) = 0 if* $P_{adh} < 0.80$, and $\beta_p x_p$ are the following covariates of interest, ranked by clinical importance:

1. COPD Exacerbation Severity at Baseline (Severe exacerbation vs. Not severe exacerbation; defined in Section 4.4.9)
2. COPD Severity at Baseline (Moderate vs. Severe/Very Severe; defined in Section 4.4.8)
3. Treatment Group (Intervention vs. Control)
4. Device Time on Study
5. Smoking Status (Current vs. Former)
6. Age
7. Sex
8. Race (White vs. Non-white)
9. Number of COPD Exacerbations During the past 12 Months Relative to Baseline
10. Prior Symbicort Treatment at Baseline (Symbicort Naïve vs. Symbicort Pre-Treated)
11. Time (months) on ICS/LABA Medication at Baseline (Less than Six Months vs. Six or More Months)

Odds ratios (OR) of these covariates and their corresponding 95% CIs will be summarized. In the event that more than seven of the above covariates are found to be significant in the univariate modeling (Step 1); starting with the least rank, covariates will be excluded in the multivariate regression model until seven covariates are left.

5.4 Secondary Analysis

All secondary analyses are done using the FAS and PP populations. Since the following analyses are considered exploratory in nature, no multiple comparison adjustments will be made.

Each secondary outcome measure will be analyzed using an ANCOVA model that follows the below general formula:

$$E(Y) = \beta_0 + \beta_1 x_1 + \ldots + \beta_p x_p$$

where $\beta_p x_p$ are the model covariates found significant from the logistic regression sensitivity analysis.

Every covariate found to be significant by the secondary outcome ANCOVA model will then be evaluated, as a sub-group analysis, by a t-test, stratified by group. For each t-test conducted the equality of variances will be tested and in the case where variances are not equal, the Satterthwaite-t test will be reported.

The subgroup analysis will only be performed if the number of subjects within each subgroup is at least five.

5.4.1 Device Time on Study

The analysis of the first secondary outcome will be the comparison of device time on study between the intervention and control groups. The number of subjects still in the study, number of drop-outs and Kaplan-Meier (KM) estimates and 95% CIs will be summarized monthly for each treatment group. Kaplan-Meier methodology will also be used to evaluate any potential differences in device time on study between treatment groups. Median device time on study, expressed as months, the corresponding 95% CI and p-value will be presented.

The device time on study, in months and days, will be presented in a listing.

5.4.2 Number of Symbicort Inhalations per Day

The analysis of the second secondary outcome will be the comparison of the mean number of Symbicort inhalations per day between the intervention and control groups. The mean number of Symbicort inhalations per day will first be computed for each subject, for the entire 26 week study period, and presented descriptively. Summary statistics will also be presented for the mean number of Symbicort inhalations per day for each of the three study intervals summarized by group and overall.

In addition, similarily to the primary endpoint analysis, the effect of medication reminders on the average Symbicort inhalations per day over the 26 week study period will be evaluated using a t-test. The equality of variances will also be tested and in the case where variances are not equal, the Satterthwaite-t test will be reported. The mean number of Symbicort inhalations per day throughout the 26 week study period will also be summarized by subject adherence (adherent vs. non-adherent subjects) and subject overdose (overdosed vs. non-overdosed subjects). The effect of medication reminders on the average Symbicort inhalations per day over the 26 week study study period will be also be evaluated using a t-test for both sub-groups. The equality of variances will also be tested and in the case where variances are not equal, the Satterthwaite t-test will be reported.

5.4.3 Number of Complete Sets of Symbicort Puffs per Day

The analysis of the third secondary outcome will be the comparison of the mean number of complete sets of Symbicort puffs per day between the intervention and control groups. The mean number of complete sets of Symbicort puffs per day will first be presented descriptively for the entire 26 week study period. Summary statistics will also be presented for the mean number of complete sets of Symbicort puffs per day for each of the three study intervals, summarized by group and overall.

In addition, the effect of medication reminders on the average number of complete sets of Symbicort puffs per day over the 26 week study period will be evaluated using a t-test. The equality of variances will also be tested and in the case where variances are not equal, the Satterthwaite-t test will be reported. The average number of complete sets of Symbicort puffs per day throughout the 26 week study period will also be summarized by subject adherence (adherent vs. non-adherent subjects) and subject overdose (overdosed vs. non-overdosed subjects). The sub-group analysis on the effect of medication reminders on the average number of complete sets of Symbicort puffs per day over the 26 week study study period will be also be evaluated using a t-test. The equality of variances will also be tested and in the case where variances are not equal, the Satterthwaite t-test will be reported.

5.4.4 Mean CCQ Scores

The analysis of the fourth secondary outcome will be the comparison of mean total and domain CCQ scores between the intervention and control groups. Baseline and EOT CCQ total and domain scores will be summarized by group, and overall. In addition, the percentage of MCID responders (defined in Section 4.4.6) will be summarized descriptively. Weekly CCQ total and domain scores will be summarized descriptively for each study week, and for each of the three study intervals for the intervention group only. The number and percentage of MCID responders will also be presented for the weekly CCQ Total scores.

To assess any potential effects of medication reminders on subject health status, an ANCOVA model will be created for each CCQ total and the three domain scores. Each model will include group, visit that the CCQ was administered, an interaction term between visit and group, and significant covariates of interest from the sensitivity analysis (as described in Section 5.3.1.2). The models will also adjust for repeated measures since subjects will fill out more than one CCQ throughout the study.

Finally, the difference in the percentage of responders to the CCQ Total Score at EOT between the two groups will be compared by a Chi-Square test. However, if any group's cell count is less than five, Fisher's exact test will be used instead.

Only subjects with both Baseline and EOT CCQ data will be included in the analysis. Responses to the individual CCQ items, the total score and the three domain scores, and whether or not a subject was a MCID responder will be provided in a listing.

5.4.5 Change from Baseline and Weekly Total and Domain CCQ Scores

The analysis of the fifth secondary outcome will be the comparison of the change in weekly total and domain CCQ scores for the intervention group, for each two month interval. Any effects of medication reminders on the change in CCQ total and the three domain scores for all the intervals specified in Section 4.2.4 will be investigated by an ANCOVA model following the format described in Section 5.4.

To further determine if there is an association between Symbicort medication adherence and change in CCQ, a Pearson correlation will be conducted between the change in CCQ scores and adherent days. For each CCQ score (total and domain), the Pearson correlation coefficient and corresponding p-value will be presented.

5.4.6 Number of Sets of Adherent Symbicort Puffs per Day at Every Two Month Interval

The analysis of the sixth secondary outcome will be the comparison of the average number of sets of adherent Symbicort puffs per day between each group, for each two month interval. The mean number of sets of Symbicort puffs per day for each of the three study intervals will be summarized by group, and overall. As defined in Section 4.4.1, each subject's device time on study day is assigned either '0' or '2', and the mean of all those '0' or '2' are computed for each subject for each of the three study intervals. Summary statistics of all subjects' mean sets of adherent Symbicort puffs per day will be presented.

Two ANCOVA models, as described in Section 5.4, will be created to assess: the between-group and within-group effects of medication reminders on only the mean number of sets of adherent Symbicort puffs per day for each study interval.

Between-Group Effects

The between-group effects model will include group, study interval, an interaction term between study interval and group, and the covariates of interest. Due to the repeated nature of the study intervals, the model will also adjust for repeated measures.

Within-Group Effects

The within-group effects model will be stratified by group in order to separately assess the mean number of sets of Symbicort puffs per day for each study interval in each group. The model will include: study interval, the covariates of interest and adjust for repeated measures.

Subjects' mean number of sets of Symbicort puffs per day for each study interval will be presented in a listing.

5.4.7 Number of Double Puffs

The analysis of the seventh secondary outcome will be the comparison of the total number of double puffs taken throughout the study between each group. The number of double puffs and proportion of double puffs will be summarized by group. The proportion of double puffs will be calculated as follows:

$$Proportion\ of\ Double\ Puffs = \frac{\frac{Total\ Number\ of\ Double\ Puffs\ Throughout\ the\ Study\ Period}{Total\ Number\ of\ Puff\ Sets\ Throughout\ the\ Study\ Period}}{Subjects's\ Total\ Device\ Time\ on\ Study}$$

To determine if the number of double puffs is different between the groups, the average number of double puffs between groups will be compared using a t-test. A t-test will also be used to evaluate if the proportion of double puffs is different between the two groups. For all t-tests, the equality of variances will also be tested and in the case where variances are not equal, the Satterthwaite-t test will be reported.

5.4.8 Number of Adherent Days

The analysis of the eighth secondary outcome will be the comparison of the total number of adherent days (Section 4.2.7, Section 4.4.1) between each group. Adherent days and the proportion of adherent days will be summarized by group, and overall for the whole 26 week treatment period. The proportion of adherent days will be also be presented by subjects' lung function at Baseline (defined in Section 4.4.8) and exacerbation risk at Baseline (defined in Section 4.4.9) using descriptive statistics.

To investigate the effects of potential confounding covariates on the relationship between medication reminders and adherent days, an ANCOVA model will be utilized. The model will include group and the covariates of interest from the sensitivity analysis, and will follow the methods described in Section 5.4.

In addition, the proportion of adherent days by subjects' lung function (better or worse) and exacerbation severity (not severe or severe) at Baseline will be compared between the two groups using a t-test. The equality of variances will also be tested and in the case where variances are not equal, the Satterthwaite-t test will be reported.

Adherent days will be presented in a listing.

5.4.9 Number of No Use Days

The analysis of the ninth secondary outcome will be the comparison of the total number of no use days between each group. No use days and the proportion of no use days will be summarized by group, and overall for the whole 26 week treatment period. Subject's proportion of no use days will be calculated as follows:

$$Proportion\ of\ No\ Use\ Days = \frac{Subject's\ Number\ of\ No\ Use\ Days}{Subject's\ Device\ Time\ on\ Study\ (days)}$$

To investigate the effects of potential confounding covariates on the relationship between medication reminders and no use days, an ANCOVA model puffs will be utilized. The model will include group and the covariates of interest from the sensitivity analysis, and will follow the methods described in Section 5.4.

The subgroup analysis will only be performed if the number of subjects within each subgroup is at least five.

No use days will be presented in a listing.

5.4.10 Number of Underuse Days

The analysis of the tenth secondary outcome will be the comparison of the total number of underuse days between each group. Underuse days and the proportion of underuse days will be summarized by group, and overall for the whole 26 week treatment period. Subject's proportion of underuse days will be calculated as follows:

$$Proportion\ of\ Underuse\ Days = \frac{Subject's\ Number\ of\ Underuse\ Days}{Subject's\ Device\ Time\ on\ Study\ (days)}$$

To investigate the effects of potential confounding covariates on the relationship between medication reminders and underuse days, an ANCOVA model will be utilized. The model will include group and the covariates of interest from the sensitivity analysis, and will follow the methods described in Section 5.4.

The subgroup analysis will only be performed if the number of subjects within each subgroup is at least five.

Underuse days will be presented in a listing.

5.4.11 Number of Overuse Days

The analysis of the eleventh secondary outcome will be the comparison of the total number of overuse days between each group. Overuse days and the proportion of overuse days will be summarized by group, and overall for the whole 26 week treatment period. Subject's proportion of overuse days will be calculated as follows:

$$Proportion\ of\ Overuse\ Days = \frac{Subject's\ Number\ of\ Overuse\ Days}{Subject's\ Device\ Time\ on\ Study\ (days)}$$

Overuse days will be presented in a listing.

5.4.12 Number of Overuse Alert Days

The analysis of the twelveth secondary outcome will be the comparison of the total number of overuse alert days between each group. Overuse alert days and the proportion of overuse alert

days will be summarized by group, and overall for the whole 26 week treatment period. Subject's proportion of overuse alert days will be calculated as follows:

$$Proportion\ of\ Overuse\ Alert\ Days = \frac{Subject's\ Number\ of\ Overuse\ Alert\ Days}{Subject's\ Device\ Time\ on\ Study\ (days)}$$

It is expected that the number and proportion of overuse alert days throughout the study will be low. Due to the expected low counts, number of overuse alert days will be combined with number of overuse days as the secondary endpoint analyzed by an ANCOVA model to investigate the effects of potential confounding covariates on the relationship between medication reminders and overuse days and overuse alert days. The model will include group and the covariates of interest from the sensitivity analysis, and will follow the methods described in Section 5.4.

The subgroup analysis will only be performed if the number of subjects within each subgroup is at least five.

Overuse alert days will be presented in a listing.

5.4.13 Number of Symbicort Prescription Fills

The analysis of the final secondary outcome will be the comparison of the number of Symbicort prescription fills between each group. Symbicort prescription fills will be summarized by group, and overall for the whole 26 week treatment period. Consideration of whether or not a subject filled their prescription occurs during device time on study with the expectation that for each 30.25 days of device time on study a subject will have one Symbicort prescription fill. The expected total number of Symbicort prescription fills will be reduced by one for those subjects who were given a supply of Symbicort at randomization. Given that not all subjects may have the same number of expected prescription fills, the number of prescription fills expressed as a percentage will also be presented. To further investigate any potential effects of medication reminders on the number of Symbicort prescription fills, an ANCOVA model will be utilized. The model will include group and the covariates of interest from the sensitivity analysis, and will follow the methods described in Section 5.4.

Pharmacy fill information will be presented in a listing.

5.5 Safety Analysis

All safety analyses will be done using the FAS population.

5.5.1 Concomitant Medication Use

The number and percentage of subjects using concomitant medications and the type of medication will be reported for the FAS population, by group and overall.

Concomitant medications will be coded by using the AstraZeneca Drug Dictionary (AZDD), version 16.2. Coded medications will be summarized by AZDD code and preferred name. AstraZeneca Drug Dictionary codes will be sorted alphabetically and then preferred names will be sorted alphabetically within each AZDD code.

Concomitant medication use will be presented in a listing.

5.5.2 Symbicort Usage

Symbicort usage throughout the 26 week treatment period includes the number of puffs (instances) taken per device time on study day, the number and percentage of subjects who have taken 'X' amount of puffs per device time on study day (where 'X' is each daily puff instance), the percentage of total device time on study days for each puff instance, the percentage of device time on study days in which subjects had greater than four puffs per day, and the cumulative percentage of device time on study days in which subjects had greater than four puffs per device time on study day. The analysis will be done using both the FAS and PP populations.

Percentage of total subject device time on study days will be calculated as follows:

$$Percent\ of\ Total\ Subject\ Device\ Time\ on\ Study\ Days = \frac{Number\ of\ Instances_i}{Total\ Subject\ Device\ Time\ on\ Study\ Days} * 100$$

Where i is the index for a given puff instance ($i = 1$ to I) per day.

Percentage of device time on study days greater than four puffs per day will be calculated as follows:

$$Percent\ of\ Study\ Days > 4\ Puffs\ per\ Day = \frac{Number\ of\ Instances\ More\ than\ 4\ Puffs\ Taken}{Total\ Subject\ Device\ Time\ on\ Study\ Days} * 100$$

5.5.3 Adverse Events

Adverse events and SAEs that occurred after the start of Symbicort will be presented in separate summary tables. Summary tables will be prepared to list the number of subjects who experienced no AEs, the number of subjects who experienced an AE at least once, and each reported AE.

Adverse events will be coded using MedDRA central coding dictionary and be grouped by SOC, which will be sorted alphabetically with PTs being sorted in order of frequency of the total column within each SOC. Each event will then be divided by severity grades (mild, moderate, and severe). A separate table, following the format described above, will summarize all SAEs that occur throughout the 26 week study period. Adverse events and SAEs that led to study discontinuation will also be presented.

All AEs for each subject, including the same event on several occasions, will be listed, giving both MedDRA PT and the original term used by the investigator, SOC, severity grade, seriousness, relation to Symbicort, onset date, and stop date. A separate listing will present the above information for all reported SAEs.

6. Data Review Meeting

The Data Review Meeting will occur approximately six to eight weeks prior to the database lock. The following tables and listings will be produced:

- Table 1.1 Subject Disposition:Screened Population
- Table 1.2 Summary of Protocol Deviations Throughout the Study: Full Analysis Set
- Table 2 Subject Demographics: Full Analysis Set
- Table 5 Medical History: Full Analysis Set
- Table 6 COPD Exacerbation History: Full Analysis Set
- Table 9.1 Kaplan-Meier Life Table for Device Time on Study: Full Analysis Set
- Table 10.1 Primary Endpoint: Average Number of Sets of Adherent Symbicort Puffs per Day Over 26 Weeks & Subgroup Analyses: Full Analysis Set
- Table 10.2 Primary Endpoint: Average Number of Sets of Adherent Symbicort Puffs per Day Over 26 Weeks & Subgroup Analyses: Per-Protocol Analysis Set
- Table 11.1.1 Percent Adherent (80% or More during Device Time on Study) Univariate Logistic Regression Sensitivity Analysis : Full Analysis Set
- Table 11.1.2 Percent Adherent (80% or More during Device Time on Study) Univariate Logistic Regression Sensitivity Analysis: Per-Protocol Analysis Set
- Table 11.2.1 Percent Adherent (80% or More during Device Time on Study) Multivariate Logistic Regression Sensitivity Analysis: Full Analysis Set
- Table 11.2.2 Percent Adherent (80% or More during Device Time on Study) Multivariate Logistic Regression Sensitivity Analysis: Per-Protocol Analysis Set
- Table 13.1 Average Number of Symbicort Inhalations per Day Over 26 Weeks: Full Analysis Set
- Table 14.1 Average Number of Complete Sets of Symbicort Puffs per Day Over 26 Weeks: Full Analysis Set
- Table 15.1 Double Puff Summary Throughout the 26 Week Study Period by Analysis Population
- Table 16.1 CCQ Total and Domain Scores: Full Analysis Set
- Table 30.1 Summary of Adherent Use: Full Analysis Set
- Table 34.1 Number of Symbicort Prescription Fills: Full Analysis Set
- Table 43 Concomitant Medications: Full Analysis Set
- Table 44.1 Symbicort Underuse, Overuse, and Overuse Alert Days During the Study: Full Analysis Set
- Figure 1 Kaplan-Meier Plot for Device Time on Study
- All 19 listings

7. Changes of Analysis from Protocol

The following table records the changes of analysis between the protocol and the SAP of the study.

Changes to analysis from protocol

SAP Section	Protocol Section	Change
3.1	8.3	The addition of a Per-Protocol Analysis Set (PP)
5.3 – 5.4	8.3.1	Analyzing the primary and secondary outcome measures using the Per-Protocol Analysis Set
4.4.6, 5.4.4	5.1.2.1	Addition of descriptive statistics and group comparison of CCQ Total Score Responders (MCID of 0.4 or more)
4.2, 5.4	8.4.2	Addition of Device Time on Study, Inhalations, Complete Puff Sets, Double Puffs, No Use Days, Underuse Days, Overuse Days, Overuse Alert Days as Secondary Outcomes
5.3.1.1	8.5.2	Addition of sensitivity analyses to the primary outcome, proportion of adherent days using 80% or more cut-off; using the significant covariates from this model as the model covariates for all secondary ANCOVA models
5.3.1.1	8.5.4	Addition of Device Time on Study as a model covariate
5.4.7 – 5.4.11	8.5.3.4	Addition of Proportion of Adherent Days, Proportion of No Use Days, Proportion of Underuse Days, Proportion of Overuse Days, Proportion of Overuse Alert Days as descriptive statistics
5.4.7	8.5.3.4	Addition of descriptive statistics and group comparison for lung function and exacerbation severity at baseline by proportion of adherent days

SAP Section	Protocol Section	Change
4.2.11, 5.4.12	2.2, 8.5.3.5	Terminology 'refills' changed to 'fills'
5.4.12	8.4.2	Change to mean number of prescription fills calculation

8. References

Clinical COPD Questionnaire website
Clinical COPD Questionnaire website. http://ccq.nl/?page_id=15. Accessed October 31, 2016.

Kon et al 2014
Kon SSC, Dilaver D, Mittal M, Nolan C, Clark AL, Canavan JL, Jones SE, Polkey MI, Man WDC The Clinical COPD Questionnaire: response to pulmonary rehabilitation and minimal clinically important difference. Thorax 2014: 69:793-798.

Simmons et al 1996
Simmons MS, Nides MA, Rand CS, Wise RA, Tashkin DP Trends in compliance with bronchodilator inhaler use between follow-up visits in a clinical trial. Chest 1996: 109:963-968.

Appendix 1. Table and Listing Shells

Table Shells

Each table produced for the D859CL00003 will have the following general layout. **Bolded text** will appear on each page of the table. Details regarding the specific table numbers, title and body content of the table, and any footnote(s) are provided in the pages that follow.

Table X. Table Title

Category/Variable	Control Group N=XXX	Intervention Group N=XXX	Total N=XXX
Category[a], n (%)			
n	xxx (xx x)	xxx (xx.x)	xxx (xx.x)
Sub-category 1	xxx (xx x)	xxx (xx.x)	xxx (xx.x)
Sub-category 2	xxx (xx x)	xxx (xx.x)	xxx (xx.x)
Sub-category 3	xxx (xx x)	xxx (xx.x)	xxx (xx.x)
Missing	xxx	xxx	xxx
Variable			
n	xxx	xxx	xxx
Mean (SD)	xxx x (x.xx)	xxx x (x xx)	xxx x (x.xx)
Median	xxx x	xxx x	xxx x
Range	xxx x, xxx.x	xxx.x, xxx x	xxx.x, xxx x
Missing	xxx	xxx	xxx

[a]Footnote. [b]Another footnote. [c]Yet another footnote.

Source Data: xxxx
Program: x:\xxx\xxx*programme*.sas (9.4) (ddmmmyyyy hh:mm)

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Table 1.1 Subject Disposition: Screened Population

	Control Group (N=XXX)	Intervention Group (N=XXX)	Total (N=XXX)
Screened	xxx	xxx	xxx
Rescreened[a]	xxx	xxx	xxx
Enrolled[b], n (%)	xxx (xx x)	xxx (xx x)	xxx (xx x)
Full Analysis Set	xxx	xxx	xxx
Per-Protocol Analysis Set	xxx	xxx	xxx
Randomized[c], n (%)	xxx (xx x)	xxx (xx x)	xxx (xx x)
Completed[c]	xxx (xx x)	xxx (xx x)	xxx (xx x)
Discontinued[c], n (%)	xxx (xx x)	xxx (xx x)	xxx (xx x)
Death[d]	xxx (xx x)	xxx (xx x)	xxx (xx x)
Device Technology Issue[d,e]	xxx (xx x)	xxx (xx x)	xxx (xx x)
Development of Study-Specific Withdrawal Criteria[d]	xxx (xx x)	xxx (xx x)	xxx (xx x)
Lost to Follow-up[d]	xxx (xx x)	xxx (xx x)	xxx (xx x)
Physician Decision[d]	xxx (xx x)	xxx (xx x)	xxx (xx x)
Screen Failure[d,f]	xxx (xx x)	xxx (xx x)	xxx (xx x)
Subject Decision[d]	xxx (xx x)	xxx (xx x)	xxx (xx x)
Study Terminated by Sponsor[d]	xxx (xx x)	xxx (xx x)	xxx (xx x)
Other[d]	xxx (xx x)	xxx (xx x)	xxx (xx x)

[a]Any subject that experienced a COPD exacerbation that required hospitalization, ER visit, or treatment with systemic steroids/antibiotics within 28 days of Visit 1or during the Run-in period. Subjects could only be rescreened once.
[b] Percentages calculated using number of screened subjects as the denominator.
[c] Percentages calculated using number of enrolled subjects as the denominator.
[d] Percentages calculated using number of discontinued subjects as the denominator.
[e]Device technology issue are issues that prevented capturing of Symbicort use data by the inhaler for 28 or more days (does not include syncing issues to the Adherium network).
[e]Subjects failed screening criteria during/after run-in period

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Table 1.2 Summary of Protocol Deviations Throughout the Study: Full Analysis Set

	FAS (N=XXX)
Number of Protocol Deviations	xxx
Number of Subjects with at Least One Protocol Deviation, n (%)	xxx (xx x)
Type of Protocol Deviation[a], n (%)	
Eligibility Criteria	xxx (xx x)
Study Conduct	xxx (xx x)
Technology Issue	xxx (xx x)
Other	xxx (xx x)
Protocol Deviation Severity[a], n (%)	
Major	xxx (xx x)
Minor	xxx (xx x)
Per- Protocol Analysis Set, n (%)	xxx (xx x)

FAS: Full Analysis Set; PP: Per-Protocol Analysis Set; FAS population consists of screened subjects who were randomized and took at least one inhalation of Symbicort during the treatment phase of the study; PP consists of FAS subjects who have met all eligibility criteria, had no major protocol deviations and had a minimum of 60 days of device time on study.
[a]Percentages are calculated using the number of protocol deviations as the denominator.

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Table 2. Demographic Characteristics: Full Analysis Set

	Control Group (N=XXX)	Intervention Group (N=XXX)	P-value	Total (N=XXX)
Age at Enrollment (years)				
n	xxx	xxx		xxx
Mean (SD)	xxx x (x xx)	xxx x (x.xx)	x.xx	xxx.x (x xx)
Median	xxx x	xxx x		xxx.x
Range	xxx x, xxx x	xxx x, xxx.x		xxx x, xxx x
Missing	xxx	xxx		xxx
Sex, n (%)			x.xx	
n	xxx	xxx		xxx
Male	xxx (xx x)	xxx (xx x)		xxx (xx x)
Female	xxx (xx x)	xxx (xx x)		xxx (xx x)
Missing	xxx	xxx		xxx
Race, n (%)			x.xx	
n	xxx	xxx		xxx
White	xxx (xx x)	xxx (xx x)		xxx (xx x)
Black or African-American	xxx (xx x)	xxx (xx x)		xxx (xx x)
Asian	xxx (xx x)	xxx (xx x)		xxx (xx x)
Native Hawaiian or Pacific Islander	xxx (xx x)	xx (xx.x)		xxx (xx x)
American Indian or American Native	xxx (xx x)	xxx (xx x)		xxx (xx x)
Other	xxx (xx x)	xxx (xx x)		xxx (xx x)
Missing	xxx	xxx		xxx

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	Control Group (N=XXX)	Intervention Group (N=XXX)	P-value	Total (N=XXX)
Ethnicity, n (%)			x xx	
n	xxx	xxx		xxx
Hispanic or Latino	xxx (xx.x)	xxx (xx x)		xxx (xx.x)
Not Hispanic or Latino	xxx (xx.x)	xxx (xx x)		xxx (xx.x)
Missing	xxx	xxx		xxx
Most Recent Post-bronchodilator FEV_1			x xx	
n	xxx	xxx		xxx
Mean (SD)	xxx x (x xx)	xxx x (x xx)		xxx x (x xx)
Median	xxx x	xxx x		xxx x
Range	xxx.x, xxx x	xxx x, xxx.x		xxx.x, xxx x
Missing	xxx	xxx		xxx
Most Recent Post-bronchodilator FEV_1/FVC Ratio			x xx	
n	xxx	xxx		xxx
Mean (SD)	xxx x (x xx)	xxx x (x xx)		xxx x (x xx)
Median	xxx x	xxx x		xxx x
Range	xxx.x, xxx x	xxx x, xxx.x		xxx.x, xxx x
Missing	xxx	xxx		xxx

Categorical characteristics were compared using a chi-square test and continuous characteristics were compared between treatment groups using a t-test.
Percentages are calculated using the number of non-missing observations (n) as the denominator.
SD: Standard Deviation

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Table 3. Vital Signs: Full Analysis Set

	BASELINE			EOT		
	Control Group (N=XXX)	Intervention Group (N=XXX)	Total (N=XXX)	Control Group (N=XXX)	Intervention Group (N=XXX)	Total (N=XXX)
Seated Pulse (beats/min)						
n	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)	xxx.x (x xx)	xxx x (x.xx)	xxx x (x.xx)	xxx x (x.xx)	xxx x (x.xx)	xxx x (x xx)
Median	xxx.x	xxx x	xxx x	xxx x	xxx x	xxx x
Range	xxx x, xxx x	xxx x, xxx x	xxx x, xxx x	xxx x, xxx.x	xxx.x, xxx x	xxx.x, xxx x
Missing	xxx	xxx	xxx	xxx	xxx	xxx
Seated Systolic Blood Pressure (mmHg)						
n	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)	xxx.x (x xx)	xxx x (x.xx)	xxx x (x.xx)	xxx x (x.xx)	xxx x (x.xx)	xxx x (x xx)
Median	xxx.x	xxx x	xxx x	xxx x	xxx x	xxx x
Range	xxx x, xxx x	xxx x, xxx x	xxx x, xxx x	xxx x, xxx.x	xxx.x, xxx x	xxx.x, xxx x
Missing	xxx	xxx	xxx	xxx	xxx	xxx
Seated Diastolic Blood Pressure (mmHg)						
n	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)	xxx.x (x xx)	xxx x (x.xx)	xxx x (x.xx)	xxx x (x.xx)	xxx x (x.xx)	xxx x (x xx)
Median	xxx.x	xxx x	xxx x	xxx x	xxx x	xxx x
Range	xxx x, xxx x	xxx x, xxx x	xxx x, xxx x	xxx x, xxx.x	xxx.x, xxx x	xxx.x, xxx x
Missing	xxx	xxx	xxx	xxx	xxx	xxx

	BASELINE			EOT		
	Control Group (N=XXX)	Intervention Group (N=XXX)	Total (N=XXX)	Control Group (N=XXX)	Intervention Group (N=XXX)	Total (N=XXX)
Respiratory Rate (breaths/min)						
n	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)	xxx x (x xx)	xxx x (x xx)	xxx x (x xx)	xxx x (x xx)	xxx x (x.xx)	xxx x (x xx)
Median	xxx x	xxx x	xxx x	xxx x	xxx x	xxx x
Range	xxx x, xxx.x	xxx.x, xxx x	xxx.x, xxx x	xxx.x, xxx x	xxx x, xxx.x	xxx.x, xxx x
Missing	xxx	xxx	xxx	xxx	xxx	xxx
Temperature (°C)						
n	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)	xxx x (x xx)	xxx x (x xx)	xxx x (x xx)	xxx x (x xx)	xxx x (x.xx)	xxx x (x xx)
Median	xxx x	xxx x	xxx x	xxx x	xxx x	xxx x
Range	xxx x, xxx.x	xxx.x, xxx x	xxx.x, xxx x	xxx.x, xxx x	xxx x, xxx.x	xxx.x, xxx x
Missing	xxx	xxx	xxx	xxx	xxx	xxx
Height[a] (cm)						
n	xxx	xxx	xxx	-	-	-
Mean (SD)	xxx x (x xx)	xxx x (x xx)	xxx x (x xx)	-	-	-
Median	xxx x	xxx x	xxx x	-	-	-
Range	xxx x, xxx.x	xxx.x, xxx x	xxx.x, xxx x	-	-	-
Missing	xxx	xxx	xxx	-	-	-

	BASELINE			EOT		
	Control Group (N=XXX)	Intervention Group (N=XXX)	Total (N=XXX)	Control Group (N=XXX)	Intervention Group (N=XXX)	Total (N=XXX)
Weight[a] (kg)						
n	xxx	xxx	xxx	-	-	-
Mean (SD)	xxx.x (x xx)	xxx x (x xx)	xxx x (x.xx)	-	-	-
Median	xxx.x	xxx x	xxx x	-	-	-
Range	xxx x, xxx x	xxx x, xxx x	xxx x, xxx x	-	-	-
Missing	xxx	xxx	xxx	-	-	-

SD: Standard Deviation, EOT: End of Treatment Visit. Baseline is the date randomization occurred. End of treatment is the latest date among assessments completed around the date the final phone/device was returned.
[a]Collected only at Baseline.

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Table 4. Physical Examination: Full Analysis Set

	Control Group (N=XXX)	Intervention Group (N=XXX)	Total (N=XXX)
Screening Physical Examination Performed, n (%)			
n	xxx	xxx	xxx
Yes	xxx (xx.x)	xxx (xx x)	xxx (xx x)
No	xxx (xx.x)	xxx (xx x)	xxx (xx x)
Missing	xxx	xxx	xxx
Relevant Past Medical Conditions, n (%)			
n	xxx	xxx	xxx
Yes	xxx (xx.x)	xxx (xx x)	xxx (xx x)
No	xxx (xx.x)	xxx (xx x)	xxx (xx x)
Missing	xxx	xxx	xxx
Relevant Past Surgeries, n (%)			
n	xxx	xxx	xxx
Yes	xxx (xx.x)	xxx (xx x)	xxx (xx x)
No	xxx (xx.x)	xxx (xx x)	xxx (xx x)
Missing	xxx	xxx	xxx
Relevant Current Medical Conditions, n (%)			
n	xxx	xxx	xxx
Yes	xxx (xx.x)	xxx (xx x)	xxx (xx x)
No	xxx (xx.x)	xxx (xx x)	xxx (xx x)
Missing	xxx	xxx	xxx

Percentages are calculated using the number of non-missing observations (n) as the denominator.

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Table 5. Medical History: Full Analysis Set

	Control Group (N=XXX)	Intervention Group (N=XXX)	Total (N=XXX)
Number of Subjects with no Medical Conditions, n (%)	xxx (xx x)	xxx (xx x)	xxx (xx x)
Number of Subjects with at Least One Medical Condition, n (%)	xxx (xx x)	xxx (xx x)	xxx (xx x)
Ongoing Medical Conditions[a]	xxx (xx x)	xxx (xx x)	xxx (xx x)
Currently Taking Medication for Condition[b]	xxx(xx x)	xxx(xx x)	xxx(xx x)
SOC 1	xxx (xx x)	xxx (xx x)	xxx (xx x)
Preferred Term 1	xxx (xx x)	xxx (xx x)	xxx (xx x)
Preferred Term 2	xxx (xx x)	xxx (xx x)	xxx (xx x)
:	:	:	:
SOC Term 2	xxx (xx x)	xxx (xx x)	xxx (xx x)
:	:	:	:
SOC Term 3	xxx (xx x)	xxx (xx x)	xxx (xx x)
:	:	:	:
…			
Missing	xxx	xxx	xxx
Not Taking Medication for Condition[b]	xxx (xx x)	xxx (xx x)	xxx (xx x)
SOC 1	xxx (xx x)	xxx (xx x)	xxx (xx x)
Preferred Term 1	xxx (xx x)	xxx (xx x)	xxx (xx x)
Preferred Term 2	xxx (xx x)	xxx (xx x)	xxx (xx x)
:	:	:	:
SOC Term 2	xxx (xx x)	xxx (xx x)	xxx (xx x)
:	:	:	:
SOC Term 3	xxx (xx x)	xxx (xx x)	xxx (xx x)
:	:	:	:
…			
Missing	xxx	xxx	xxx

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	Control Group (N=XXX)	Intervention Group (N=XXX)	Total (N=XXX)
Resolved Medical Condition[a]	xxx (xx x)	xxx (xx x)	xxx (xx x)
Currently Taking Medication for Condition[c]	xxx(xx x)	xxx(xx x)	xxx(xx x)
SOC 1	xxx (xx x)	xxx (xx x)	xxx (xx x)
Preferred Term 1	xxx (xx x)	xxx (xx x)	xxx (xx x)
Preferred Term 2	xxx (xx x)	xxx (xx x)	xxx (xx x)
:	:	:	:
SOC Term 2	xxx (xx x)	xxx (xx x)	xxx (xx x)
:	:	:	:
SOC Term 3	xxx (xx x)	xxx (xx x)	xxx (xx x)
:	:	:	:
…			
Missing	xxx	xxx	xxx
Not Taking Medication for Condition[c]	xxx (xx x)	xxx (xx x)	xxx (xx x)
SOC 1	xxx (xx x)	xxx (xx x)	xxx (xx x)
Preferred Term 1	xxx (xx x)	xxx (xx x)	xxx (xx x)
Preferred Term 2	xxx (xx x)	xxx (xx x)	xxx (xx x)
:	:	:	:
SOC Term 2	xxx (xx x)	xxx (xx x)	xxx (xx x)
:	:	:	:
SOC Term 3	xxx (xx x)	xxx (xx x)	xxx (xx x)
:	:	:	:
…			
Missing	xxx	xxx	xxx

Medical conditions are coded as per MedDRA Version 19.1
Percentages are calculated using the number of non-missing observations (n) as the denominator.
[a]Percentages are based on the total number of medical conditions reported.
[b]Percentages are based on the number of ongoing medical conditions reported.
[c]Percentages are based on the number of resolved medical conditions reported.

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Table 6. COPD Exacerbation History at Baseline: Full Analysis Set

	Control Group (N=XXX)	Intervention Group (N=XXX)	Total (N=XXX)
Number of COPD Exacerbations Within the Last 12 Months [a]			
n	xxx	xxx	xxx
Mean (SD)	xxx.x (x xx)	xxx x (x xx)	xxx.x (x xx)
Median	xxx.x	xxx x	xxx.x
Range	xxx x, xxx x	xxx.x, xxx x	xxx x, xxx x
Missing	xxx	xxx	xxx
Subject Hospitalized for >24 Hours for any Exacerbation Within the Last 12 Months, n (%)			
n	xxx	xxx	xxx
Yes	xxx (xx x)	xxx (xx x)	xxx (xx x)
No	xxx (xx x)	xxx (xx x)	xxx (xx x)
Missing	xxx	xxx	xxx
Current COPD Medication Type, n (%)			
n	xxx	xxx	xxx
Antibiotics	xxx (xx x)	xxx (xx x)	xxx (xx x)
Steroids	xxx (xx x)	xxx (xx x)	xxx (xx x)
Antibiotics and Steroids	xxx (xx x)	xxx (xx x)	xxx (xx x)
Other	xxx (xx x)	xxx (xx x)	xxx (xx x)
Missing	xxx	xxx	xxx
Current COPD Severity, n (%)			
n	xxx	xxx	xxx
Moderate	xxx (xx x)	xxx (xx x)	xxx (xx x)
Severe	xxx (xx x)	xxx (xx x)	xxx (xx x)
Very Severe	xxx (xx x)	xxx (xx x)	xxx (xx x)
Missing	xxx	xxx	xxx

Percentages are calculated using the number of non-missing observations (n) as the denominator.
SD: Standard Deviation

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Table 7. Smoking History at Baseline: Full Analysis Set

	Control Group (N=XXX)	Intervention Group (N=XXX)	Total (N=XXX)
Smoker Status, n (%)			
n	xxx	xxx	xxx
Current	xxx (xx x)	xxx (xx x)	xxx (xx x)
Former	xxx (xx x)	xxx (xx x)	xxx (xx x)
Missing	xxx	xxx	xxx
Number of Packs/Day			
n	xxx	xxx	xxx
Mean (SD)	xxx.x (x xx)	xxx x (x.xx)	xxx x (x xx)
Median	xxx.x	xxx x	xxx x
Range	xxx x, xxx x	xxx x, xxx.x	xxx x, xxx x
Missing	xxx	xxx	xxx
Number of Years Cigarettes Consumed			
n	xxx	xxx	xxx
Mean (SD)	xxx.x (x xx)	xxx x (x.xx)	xxx x (x xx)
Median	xxx.x	xxx x	xxx x
Range	xxx x, xxx x	xxx x, xxx.x	xxx x, xxx x
Missing	xxx	xxx	xxx

	Control Group (N=XXX)	Intervention Group (N=XXX)	Total (N=XXX)
Number of Pack Years			
n	xxx	xxx	xxx
Mean (SD)	xxx.x (x xx)	xxx x (x.xx)	xxx.x (x xx)
Median	xxx.x	xxx x	xxx.x
Range	xxx x, xxx x	xxx x, xxx x	xxx x, xxx x
Missing	xxx	xxx	xxx

[a] Number of COPD exacerbations within the last 12 months irrespective of whether or not it required hospitalization.
Percentages are calculated using the number of non-missing observations (n) as the denominator.
SD: Standard Deviation

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Table 8.1 Subject BreatheMate User Satisfaction Survey: Full Analysis Set

Question Number		Intervention Group (N=XXX)
	Part 1: BreatheMate Mobile App	
	BreatheMate mobile app use, n (%)	
	n	xxx
	Yes	xxx (xx x)
	No	xxx (xx x)
	Missing	xxx
1	The BreatheMate app was easy to use, n (%)	
	n	xxx
	Strongly disagree	xxx (xx x)
	Disagree	xxx (xx x)
	Indifferent	xxx (xx x)
	Agree	xxx (xx x)
	Strongly agree	xxx (xx x)
	Missing	xxx
2	I did not have any technical difficulties in using the app and phone, n (%)	
	n	xxx
	Strongly disagree	xxx (xx x)
	Disagree	xxx (xx x)
	Indifferent	xxx (xx x)
	Agree	xxx (xx x)
	Strongly agree	xxx (xx x)
	Missing	xxx

Question Number		Intervention Group (N=XXX)
3	The BreatheMate app has a suitable number of options to tailor how I would like to receive my reminders, n (%)	
	n	xxx
	Strongly disagree	xxx (xx x)
	Disagree	xxx (xx x)
	Indifferent	xxx (xx x)
	Agree	xxx (xx x)
	Strongly agree	xxx (xx x)
	Missing	xxx
4	The BreatheMate app has a clean, uncluttered design, n (%)	
	n	xxx
	Strongly disagree	xxx (xx x)
	Disagree	xxx (xx x)
	Indifferent	xxx (xx x)
	Agree	xxx (xx x)
	Strongly agree	xxx (xx x)
	Missing	xxx
5	The medication reminders were helpful to ensure I was taking my medication as prescribed, n (%)	
	n	xxx
	Strongly disagree	xxx (xx x)
	Disagree	xxx (xx x)
	Indifferent	xxx (xx x)
	Agree	xxx (xx x)
	Strongly agree	xxx (xx x)
	Missing	xxx

Part 2: SmartTouch Symbicort Device

Question Number		Intervention Group (N=XXX)
	SmartTouch Symbicort device use, n (%)	
	n	xxx
	Yes	xxx (xx x)
	No	xxx (xx x)
	Missing	xxx
1	SmartTouch Symbicort device is easy to use, n (%)	
	n	xxx
	Strongly disagree	xxx (xx x)
	Disagree	xxx (xx x)
	Indifferent	xxx (xx x)
	Agree	xxx (xx x)
	Strongly agree	xxx (xx x)
	Missing	xxx
2	SmartTouch Symbicort device has all the features I expected it to have, n (%)	
	n	xxx
	Strongly disagree	xxx (xx x)
	Disagree	xxx (xx x)
	Indifferent	xxx (xx x)
	Agree	xxx (xx x)
	Strongly agree	xxx (xx x)
	Missing	xxx

Question Number		Intervention Group (N=XXX)
3	The visual and audio reminders on the device were helpful to ensure I was taking my medication as prescribed, n (%)	
	n	xxx
	Strongly disagree	xxx (xx x)
	Disagree	xxx (xx x)
	Indifferent	xxx (xx x)
	Agree	xxx (xx x)
	Strongly agree	xxx (xx x)
	Missing	xxx
4	The SmartTouch Symbicort device was easy to take on and off of my Symbicort medication, n (%)	
	n	xxx
	Strongly disagree	xxx (xx x)
	Disagree	xxx (xx x)
	Indifferent	xxx (xx x)
	Agree	xxx (xx x)
	Strongly agree	xxx (xx x)
	Missing	xxx
5	SmartTouch Symbicort device has a great look and feel, n (%)	
	n	xxx
	Strongly disagree	xxx (xx x)
	Disagree	xxx (xx x)
	Indifferent	xxx (xx x)
	Agree	xxx (xx x)
	Strongly agree	xxx (xx x)
	Missing	xxx

Percentages are calculated using the number of non-missing observations (n) as the denominator.

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Table 8.2 Investigator and Study Coordinator BreatheMate User Satisfaction Survey

Question Number		Responders (N=XXX)
	BreatheMate web portal use, n (%)	
	n	xxx
	Yes	xxx (xx x)
	No	xxx (xx x)
	Missing	xxx
1	The BreatheMate web portal is easy to use, n (%)	
	n	xxx
	Strongly disagree	xxx (xx x)
	Disagree	xxx (xx x)
	Indifferent	xxx (xx x)
	Agree	xxx (xx x)
	Strongly agree	xxx (xx x)
	Missing	xxx
2	The BreatheMate web portal has all the features I expected it to have, n (%)	
	n	xxx
	Strongly disagree	xxx (xx x)
	Disagree	xxx (xx x)
	Indifferent	xxx (xx x)
	Agree	xxx (xx x)
	Strongly agree	xxx (xx x)
	Missing	xxx

Question Number		Responders (N=XXX)
3	I could complete/view tasks in the BreatheMate web portal with a minimum number of clicks, n (%)	
	n	xxx
	Strongly disagree	xxx (xx x)
	Disagree	xxx (xx x)
	Indifferent	xxx (xx x)
	Agree	xxx (xx x)
	Strongly agree	xxx (xx x)
	Missing	xxx
4	The BreatheMate web portal has a clean, uncluttered design, n (%)	
	n	xxx
	Strongly disagree	xxx (xx x)
	Disagree	xxx (xx x)
	Indifferent	xxx (xx x)
	Agree	xxx (xx x)
	Strongly agree	xxx (xx x)
	Missing	xxx
5	The information provided by the BreatheMate web portal is easy to find and to understand, n (%) (including graphs)	
	n	xxx
	Strongly disagree	xxx (xx x)
	Disagree	xxx (xx x)
	Indifferent	xxx (xx x)
	Agree	xxx (xx x)
	Strongly agree	xxx (xx x)
	Missing	xxx

Question Number		Responders (N=XXX)
6	The BreatheMate reminders improve patient compliance with their daily ICS/LABA medication, n (%)	
	n	xxx
	Strongly disagree	xxx (xx x)
	Disagree	xxx (xx x)
	Indifferent	xxx (xx x)
	Agree	xxx (xx x)
	Strongly agree	xxx (xx x)
	Missing	xxx
7	The BreatheMate service improves medication refills, n (%)	
	n	xxx
	Strongly disagree	xxx (xx x)
	Disagree	xxx (xx x)
	Indifferent	xxx (xx x)
	Agree	xxx (xx x)
	Strongly agree	xxx (xx x)
	Missing	xxx
8	The BreatheMate service would be useful to me in helping patients to manage their condition, n (%)	
	n	xxx
	Strongly disagree	xxx (xx x)
	Disagree	xxx (xx x)
	Indifferent	xxx (xx x)
	Agree	xxx (xx x)
	Strongly agree	xxx (xx x)
	Missing	xxx

Percentages are calculated using the number of non-missing observations (n) as the denominator.

Table 9.1 Kaplan Meier Life Table for Device Time on Study: Full Analysis Set

	Control Group (N=XXX)			Intervention Group (N=XXX)		
Duration	No.Subjects	No. Drop-outs	K-M Estimate (95% CI)	No.Subjects	No. Drop-outs	K-M Estimate (95% CI)
0	xxx	xxx	xxx.x (xxx x, xxx x)	xxx	xxx	xxx x (xxx.x, xxx.x)
0 to Less Than 1 Month	xxx	xxx	xxx.x (xxx x, xxx x)	xxx	xxx	xxx x (xxx.x, xxx.x)
1 to Less Than 2 Months	xxx	xxx	xxx.x (xxx x, xxx x)	xxx	xxx	xxx x (xxx.x, xxx.x)
2 to Less Than 3 Months	xxx	xxx	xxx.x (xxx x, xxx x)	xxx	xxx	xxx x (xxx.x, xxx.x)
3 to Less Than 4 Months	xxx	xxx	xxx.x (xxx x, xxx x)	xxx	xxx	xxx x (xxx.x, xxx.x)
4 Less Than 5 Months	xxx	xxx	xxx.x (xxx x, xxx x)	xxx	xxx	xxx x (xxx.x, xxx.x)
5 Less Than 6 Months	xxx	xxx	xxx.x (xxx x, xxx x)	xxx	xxx	xxx x (xxx.x, xxx.x)
6 Months	xxx	xxx	xxx.x (xxx x, xxx x)	xxx	xxx	xxx x (xxx.x, xxx.x)
Median Device Time on Study (Months)			xxx.x			xxx x
95% CI for Difference in Time			(xxx.x, xxx x)			
P-value			x.xx			

Table 9.2 Kaplan Meier Life Table for Device Time on Study: Per-Protocol Analysis Set
Follow the format of Table 9.1 but with PP

Table 10.1 Primary Endpoint: Average Number of Sets of Adherent Symbicort Puffs per Day Over 26 Weeks & Subgroup Analyses: Full Analysis Set

	Sets of Puffs per Day					
	N	Mean (SD)	Median	Range	Missing	P-value
Control Group	xxx	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	x.xx*
Intervention Group	xxx	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	
Subgroup Analyses						
Adherent Subjects[a]	xxx	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	x xx
Non-adherent Subjects	xxx	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	
Overdose Subjects[b]	xxx	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	x xx
Non-overdose Subjects	xxx	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	

T-test p-values are reported; SD: Standard Deviation;*Indicates the Satterthwaite t-static is reported; [a]A subject is considered adherent if they had a proportion of 80% or more adherent days during device time on study.; [b]A subject is considered to have overdosed on Symbicort if on the Overdose CRF, the question "Any Symbicort overdoses?' is answered 'Yes' for any day during the study.

Table 10.2 Primary Endpoint: Average Number of Sets of Adherent Symbicort Puffs per Day Over 26 Weeks & Subgroup Analyses: Per-Protocol Analysis Set

Use the same format as Table 10.1, but with PP

Table 11.1.1 Percent Adherent (80% or More during Device Time on Study) Univariate Logistic Regression Sensitivity Analysis : Full Analysis Set

	FAS Population (N=XXX)	
Covariate	Odds Ratio (95% CI)	P-value
Age at Enrollment	xx xxx (xx xxx, xx xxx)	x.xxx
Race		
White	Reference Group	
Non-White	xx xxx (xx xxx, xx xxx)	x.xxx
Sex		
Male	Reference Group	
Female	xx xxx (xx xxx, xx xxx)	x.xxx
Smoking Status		
Current	Reference Group	
Former	xx xxx (xx xxx, xx xxx)	x.xxx
Number of COPD Exacerbations	xx xxx (xx xxx, xx xxx)	x.xxx

Covariate	FAS Population (N=XXX) Odds Ratio (95% CI)	P-value
COPD Exacerbation Severity		
Moderate	Reference Group	
Severe/Very Severe	xx xxx (xx xxx, xx xxx)	x xxx
Group		
Control	Reference Group	
Intervention	xx xxx (xx xxx, xx xxx)	x xxx
Device Time	xx xxx (xx xxx, xx xxx)	x xxx

Logistic regression model based odds ratios are reported; CI: Confidence Interval
COPD Severity Level: Moderate is FEV1 % predicted 50 – 79% , Severe/Very Severe is FEV1 % predicted < 50%

Table 11.1.2 Percent Adherent (80% or More during Device Time on Study) Univariate Logistic Regression Sensitivity Analysis: Per-Protocol Analysis Set
Use the same format as Table 11.1.1, but with PP

Table 11.2.1 Percent Adherent (80% or More during Device Time on Study) Multivariate Logistic Regression Sensitivity Analysis: Full Analysis Set

	FAS Population (N=XXX)	
Covariate	Odds Ratio (95% CI)	P-value
Age at Enrollment	xx xxx (xx xxx, xx xxx)	x.xxx
Race		
White	Reference Group	
Non-White	xx xxx (xx xxx, xx xxx)	x.xxx
Sex		
Male	Reference Group	
Female	xx xxx (xx xxx, xx xxx)	x.xxx
Smoking Status		
Current	Reference Group	
Former	xx xxx (xx xxx, xx xxx)	x.xxx
Number of COPD Exacerbations	xx xxx (xx xxx, xx xxx)	x.xxx

Covariate	FAS Population (N=XXX) Odds Ratio (95% CI)	P-value
COPD Exacerbation Severity		
Moderate	Reference Group	
Severe/Very Severe	xx xxx (xx xxx, xx xxx)	x xxx
Group		
Control	Reference Group	
Intervention	xx xxx (xx xxx, xx xxx)	x xxx
Device Time	xx xxx (xx xxx, xx xxx)	x xxx

A multivariate logistic regression analysis using covariates that were significant at the 0.25 level from the univariate logistic regression analysis (Table 11.1.1) was done. Above covariates are those that were significant at the 0.15 level. CI: Confidence Interval, COPD Severity Level: Moderate is FEV1 % predicted 50 – 79%, Severe/Very Severe is FEV1 % predicted < 50%.

Table 11.2.2 Percent Adherent (80% or More during Device Time on Study) Multivariate Logistic Regression Sensitivity Analysis: Per-Protocol Analysis Set

Use the same format as Table 11.2.1, but with PP with the footnote reading….A multivariate logistic regression analysis using covariates that were significant at the 0.25 level from the univariate logistic regression analysis (Table 11.2.1) was done. Above covariates are those that were significant at the 0.15 level. CI: Confidence Interval, COPD Severity Level: Moderate is FEV1 % predicted 50 – 79%, Severe/Very Severe is FEV1 % predicted < 50%.

Every covariate found to be significant by the multivariate logistic regression sensitivity analysis (Table 11.2.1) will then be included in the below subgroup analyses (Table 12.1). If any continuous covariate is found to be significant by the multivariate logistic regression model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available. (See shell on next page)

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Table 12.1 Average Number of Sets of Adherent Symbicort Puffs per Day Over 26 Weeks Additional Subgroup Analyses[a]: Full Analysis Set

	Sets of Puffs per Day					
	N	Mean (SD)	Median	Range	Missing	P-value
COVARIATE A						
SUBGROUP 1	xxx					
Control Group, n(%)	xxx (xx.x)	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	x.xx*
Intervention Group, n(%)	xxx (xx.x)	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	
SUBGROUP 2	xxx					
Control Group, n(%)	xxx (xx.x)	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	x xx
Intervention Group, n(%)	xxx (xx.x)	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	
COVARIATE B						
SUBGROUP 1	xxx					
Control Group, n(%)	xxx (xx.x)	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	x xx
Intervention Group, n(%)	xxx (xx.x)	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	
SUBGROUP 2	xxx					
Control Group, n(%)	xxx (xx.x)	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	x xx
Intervention Group, n(%)	xxx (xx.x)	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	
…						

T-test p-values are reported, SD: Standard Deviation
*Indicates the Satterthwaite t-static is reported.
Covariates were determined by demonstrating a significance level of 0.05 or less from the Adherent Symbicort Sensitivity analysis logisitic regression model (Table 12.1).

Table 12.2 Average Number of Sets of Adherent Symbicort Puffs per Day Over 26 Weeks Additional Subgroup Analyses[a]: Per-Protocol Analysis Set

For every covariate found to be significant in the multivariate logistic regression sensitivity analysis presented in Table 11.2.2 will then be included in the subgroup analyses. If any continuous covariate is found to be significant by the multivariate logistic regression model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available. This table will use the same format as Table 12.1, but with PP.

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Table 13.1 Average Number of Symbicort Inhalations per Day Over 26 Weeks: Full Analysis Set

	Inhalations per Day					
	N	Mean (SD)	Median	Range	Missing	P-value
Control Group	xxx	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	x.xx*
Intervention Group	xxx	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	
Subgroup Analyses						
Adherent Subjects[a]	xxx	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	x xx
Non-adherent Subjects	xxx	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	
Overdose Subjects[b]	xxx	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	x xx
Non-overdose Subjects	xxx	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	

The actual number of Symbicort inhalations on a given day was used in the analysis.
T-test p-values are reported; SD: Standard Deviation;*Indicates the Satterthwaite t-static is reported; [a]A subject is considered adherent if they maintained the dosing regimen of taking exactly two sets of two Symbicort puffs per day, four puffs total, 80% or more during device time on study; [b]A subject is considered to have overdosed on Symbicort if on the Overdose CRF, the question ‘‘Any Symbicort overdoses?’ is answered ‘Yes’ for any day during the study.

Table 13.2 Average Number of Symbicort Inhalations per Day Over 26 Weeks: Per-Protocol Analysis Set
Use the same format as Table 13.1, but with PP

Table 14.1 Average Number of Complete Sets of Symbicort Puffs per Day Over 26 Weeks: Full Analysis Set

	Complete Sets per Day					
	N	Mean (SD)	Median	Range	Missing	P-value
Control Group	xxx	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	x.xx*
Intervention Group	xxx	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	
Subgroup Analyses						
Adherent Subjects[a]	xxx	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	x xx
Non-adherent Subjects	xxx	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	
Overdose Subjects[b]	xxx	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	x xx
Non-overdose Subjects	xxx	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	

A complete set of Symbicort is two Symbicort puffs that are taken within 60 minutes of each other, for a given day. T-test p-values are reported; SD: Standard Deviation, *Indicates the Satterthwaite t-static is reported; [a]A subject is considered adherent if they maintained the dosing regimen of taking exactly two sets of two Symbicort puffs per day, four puffs total, 80% or more during device time on study; [b]A subject is considered to have overdosed on Symbicort if on the Overdose CRF, the question "Any Symbicort overdoses?' is answered 'Yes' for any day during the study.

Table 14.2 Average Number of Complete Sets of Symbicort Puffs per Day Over 26 Weeks: Per-Protocol Analysis Set
Use the same format as Table 14.1, but with PP

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Table 15 Double Puff Summary Over 26 Week Study Period by Treatment Group by Analysis Population

	FAS Population (N=XXX)			PP Population (N=XXX)		
	Control Group (N=XXX)	Intervention Group (N=XXX)	P-value*	Control Group (N=XXX)	Intervention Group (N=XXX)	P-value
Number of Double Puffs[a] [X]						
n	xxx	xxx		xxx	xxx	
Mean (SD)	xxx.x (x xx)	xxx x (x.xx)	x xxx	xxx x (x.xx)	xxx x (x xx)	x.xxx*
Median	xxx.x	xxx x		xxx x	xxx x	
Range	xxx x, xxx x	xxx x, xxx.x		xxx x, xxx.x	xxx x, xxx.x	
Missing	xxx	xxx		xxx	xxx	
Total Number of Puff Sets[b] [Y]						
n	xxx	xxx		xxx	xxx	
Mean (SD)	xxx.x (x xx)	xxx x (x.xx)	x xxx	xxx x (x xx)	xxx x (x xx)	x xxx
Median	xxx.x	xxx x		xxx x	xxx x	
Range	xxx x, xxx x	xxx x, xxx.x		xxx x, xxx.x	xxx x, xxx.x	
Missing	xxx	xxx		xxx	xxx	
Total Number of Subject Days[c] [Z]						
n	xxx	xxx		xxx	xxx	
Mean (SD)	xxx.x (x xx)	xxx x (x.xx)	x xxx	xxx x (x.xx)	xxx x (x xx)	x xxx
Median	xxx.x	xxx x		xxx x	xxx x	
Range	xxx x, xxx x	xxx x, xxx.x		xxx x, xxx.x	xxx x, xxx.x	
Missing	xxx	xxx		xxx	xxx	

	FAS Population (N=XXX)			PP Population (N=XXX)		
	Control Group (N=XXX)	Intervention Group (N=XXX)	P-value*	Control Group (N=XXX)	Intervention Group (N=XXX)	P-value
X / Y / Z						
n	xxx	xxx		xxx	xxx	
Mean (SD)	xxx x (x.xx)	xxx.x (x xx)	x xxx	xxx.x (x xx)	xxx x (x xx)	x xxx*
Median	xxx x	xxx.x		xxx.x	xxx x	
Range	xxx x, xxx.x	xxx x, xxx x		xxx x, xxx x	xxx x, xxx x	
Missing	xxx	xxx		xxx	xxx	

FAS: Full Analysis Set; PP: Per-Protocol Set; SD: Standard Deviation; T-test p-values are reported; *Indicates the Satterthwaite t-static is reported.
[a]A double puff is two puffs taken within one second of each other; [b]The total number of puffs sets is the total number of all puff sets taken by a subject throughout the 26 week study period; [c]Total number of subject days is the total device time on study for a subject.

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Table 16.1 CCQ Total and Domain Scores: Full Analysis Set

	BASELINE			EOT		
	Control Group (N=XXX)	Intervention Group (N=XXX)	Total (N=XXX)	Control Group (N=XXX)	Intervention Group (N=XXX)	Total (N=XXX)
CCQ Total Score						
n	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)	xxx.x (x xx)	xxx.x (x xx)	xxx x (x xx)	xxx x (x xx)	xxx.x (x xx)	xxx.x (x xx)
Median	xxx.x	xxx.x	xxx x	xxx x	xxx.x	xxx.x
Range	xxx x, xxx x	xxx x, xxx x	xxx x, xxx.x	xxx.x, xxx x	xxx x, xxx x	xxx x, xxx x
Missing	xxx	xxx	xxx	xxx	xxx	xxx
CCQ Total Score Responders[a], n (%)	NA	NA	NA			
Yes	-	-	-	xxx (xx x)	xxx (xx x)	xxx (xx x)
No	-	-	-	xxx (xx x)	xxx (xx x)	xxx (xx x)
Missing	-	-	-	xxx	xxx	xxx
P-value[b]			-			x.xxx
Symptom Score						
n	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)	xxx.x (x xx)	xxx.x (x xx)	xxx x (x xx)	xxx x (x xx)	xxx.x (x xx)	xxx.x (x xx)
Median	xxx.x	xxx.x	xxx x	xxx x	xxx.x	xxx.x
Range	xxx x, xxx x	xxx x, xxx x	xxx x, xxx.x	xxx.x, xxx x	xxx x, xxx x	xxx x, xxx x
Missing	xxx	xxx	xxx	xxx	xxx	xxx
Functional State Score						
n	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)	xxx.x (x xx)	xxx.x (x xx)	xxx x (x xx)	xxx x (x xx)	xxx.x (x xx)	xxx.x (x xx)
Median	xxx.x	xxx.x	xxx x	xxx x	xxx.x	xxx.x
Range	xxx x, xxx x	xxx x, xxx x	xxx x, xxx.x	xxx.x, xxx x	xxx x, xxx x	xxx x, xxx x
Missing	xxx	xxx	xxx	xxx	xxx	xxx

	BASELINE			EOT		
	Control Group (N=XXX)	Intervention Group (N=XXX)	Total (N=XXX)	Control Group (N=XXX)	Intervention Group (N=XXX)	Total (N=XXX)
Mental State Score						
n	xxx	xxx	xxx	xxx	xxx	xxx
Mean (SD)	xxx.x (x xx)	xxx.x (x xx)	xxx x (x.xx)	xxx.x (x xx)	xxx x (x.xx)	xxx.x (x xx)
Median	xxx.x	xxx.x	xxx x	xxx.x	xxx x	xxx.x
Range	xxx x, xxx x	xxx x, xxx x	xxx x, xxx x	xxx x, xxx x	xxx x, xxx.x	xxx x, xxx x
Missing	xxx	xxx	xxx	xxx	xxx	xxx

SD: Standard Deviation, EOT: End of Treatment Visit, CCQ: Clinical COPD Questionnaire; NA: Not Applicable. CCQ Scores range from 0 – 6, with higher values indicative of poorer health status. Baseline is the date randomization occurred; End of treatment is the latest date among assessments completed around the date the final phone/device was returned.
[a]A responder is a subject who experienced a decrease of at least 0.4 units from the Baseline CCQ Total score.
[b]Chi-Square p-values are reported.

Table 16.2 CCQ Total and Domain Scores: Per-Protocol Analysis Set
Use the same format as Table 16.1, but with PP

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Table 17.1 CCQ Total and Domain Scores ANCOVA Model Results: Full Analysis Set

	CCQ Total Score (N=XXX)		CCQ Symptom Score (N=XXX)		CCQ Functional State Score (N=XXX)		CCQ Mental State Score (N=XXX)	
Covariate	Mean (95% CI)	P-value	Mean (95% CI)	P-value	Mean (95% CI)	P-value	Mean (95% CI)	P-value
Age at Enrollment	xxx x (xxx.x, xxx x)	x xx	xxx x (xxx.x, xxx x)	x xx	xxx.x (xxx x, xxx.x)	x.xx	xxx.x (xxx x, xxx.x)	x xx
Race								
White	xxx x (xxx.x, xxx x)	x xx	xxx x (xxx.x, xxx x)	x xx	xxx x (xxx x, xxx.x)	x.xx	xxx.x (xxx x, xxx.x)	x xx
Non-White	xxx x (xxx.x, xxx x)	x xx	xxx x (xxx.x, xxx x)	x xx	xxx.x (xxx x, xxx.x)	x.xx	xxx.x (xxx x, xxx.x)	x xx
Sex								
Male	xxx x (xxx.x, xxx x)	x xx	xxx x (xxx.x, xxx x)	x xx	xxx x (xxx x, xxx.x)	x.xx	xxx.x (xxx x, xxx.x)	x xx
Female	xxx x (xxx.x, xxx x)	x xx	xxx x (xxx.x, xxx x)	x xx	xxx.x (xxx x, xxx.x)	x.xx	xxx.x (xxx x, xxx.x)	x xx
Smoking Status								
Current	xxx x (xxx.x, xxx x)	x xx	xxx x (xxx.x, xxx x)	x xx	xxx x (xxx x, xxx.x)	x.xx	xxx.x (xxx x, xxx.x)	x xx
Former	xxx x (xxx.x, xxx x)	x xx	xxx x (xxx.x, xxx x)	x xx	xxx.x (xxx x, xxx.x)	x.xx	xxx.x (xxx x, xxx.x)	x xx
Number of COPD Exacerbations	xxx x (xxx.x, xxx x)	x xx	xxx x (xxx.x, xxx x)	x xx	xxx.x (xxx x, xxx.x)	x.xx	xxx.x (xxx x, xxx.x)	x xx

Covariate	CCQ Total Score (N=XXX) Mean (95% CI)	P-value	CCQ Symptom Score (N=XXX) Mean (95% CI)	P-value	CCQ Functional State Score (N=XXX) Mean (95% CI)	P-value	CCQ Mental State Score (N=XXX) Mean (95% CI)	P-value
COPD Exacerbation Severity								
Moderate	xxx.x (xxx x, xxx x)	x xx	xxx x (xxx x, xxx x)	x.xx	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx.x, xxx x)	x.xx
Severe/Very Severe	xxx.x (xxx x, xxx x)	x xx	xxx x (xxx x, xxx x)	x.xx	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx.x, xxx x)	x.xx
Prior Symbicort Treatment								
Symbicort Naïve	xxx.x (xxx x, xxx x)	x xx	xxx x (xxx x, xxx x)	x.xx	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx.x, xxx x)	x.xx
Symbicort Pre-treated	xxx.x (xxx x, xxx x)	x xx	xxx x (xxx x, xxx x)	x.xx	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx.x, xxx x)	x.xx
Time (months) on ICS/LABA Medication at Baseline								
Less than Six Months	xxx.x (xxx x, xxx x)	x xx	xxx x (xxx x, xxx x)	x.xx	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx.x, xxx x)	x.xx
Six or More Months	xxx.x (xxx x, xxx x)	x xx	xxx x (xxx x, xxx x)	x.xx	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx.x, xxx x)	x.xx
Group								
Control	xxx.x (xxx x, xxx x)	x xx	xxx x (xxx x, xxx x)	x.xx	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx.x, xxx x)	x.xx
Intervention	xxx.x (xxx x, xxx x)	x xx	xxx x (xxx x, xxx x)	x.xx	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx.x, xxx x)	x.xx
Visit								
Baseline	xxx.x (xxx x, xxx x)	x xx	xxx x (xxx x, xxx x)	x.xx	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx.x, xxx x)	x.xx
EOT	xxx.x (xxx x, xxx x)	x xx	xxx x (xxx x, xxx x)	x.xx	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx.x, xxx x)	x.xx
Visit*Group	xxx.x (xxx x, xxx x)	x xx	xxx x (xxx x, xxx x)	x.xx	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx.x, xxx x)	x.xx
Device Time	xxx.x (xxx x, xxx x)	x xx	xxx x (xxx x, xxx x)	x.xx	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx.x, xxx x)	x.xx

ANCOVA model based means are reported, Candidate covariates for the ANCOVA model were the significant covariates from the Adherent Symbicort Sensitivity analysis (Table 11.2.1). CCQ: Clinical COPD Questionnaire, CI: Confidence Interval, EOT: End of Treatment Visit. Baseline is the date randomization occurred; End of treatment is the latest date among assessments completed around the date the final phone/device was returned. CCQ Scores range from 0 – 6, with higher values indicative or poorer health status. COPD Severity Level: Moderate is FEV1 % predicted 50 – 79%, Severe/Very Severe is FEV1 % predicted < 50%.

Please note that for all secondary outcome ANCOVA models, depending on the results of the sensitivity analysis of primary outcome, the logistic regression model, not all covariates listed here will be included in the final table (only those that were significant in the logistic regression model).

Table 17.2 CCQ Total and Domain Scores ANCOVA Model Results: Per-Protocol Analysis Set
Use same format as Table 17.1, but using the significant covariates from the model in Table 11.2.2. *Note: footnote will call out Table 11.2.2, instead*

Every covariate found to be significant in the CCQ Total Score ANCOVA model presented in Table 17.1 will then be included in the below subgroup analyses. If any continuous covariate is found to be significant by the secondary outcome ANCOVA model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available.

Table 18.1.1 CCQ Total Score Sub-Group Analyses[a]: Full Analysis Set

	CCQ Total Score					
	N	Mean (SD)	Median	Range	Missing	P-value
COVARIATE A						
SUBGROUP 1	xxx					
Control Group, n(%)	xxx (xx.x)	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	x.xx*
Intervention Group, n(%)	xxx (xx.x)	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	
SUBGROUP 2	xxx					
Control Group, n(%)	xxx (xx.x)	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	x xx
Intervention Group, n(%)	xxx (xx.x)	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	
COVARIATE B						
SUBGROUP 1	xxx					
Control Group, n(%)	xxx (xx.x)	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	x xx
Intervention Group, n(%)	xxx (xx.x)	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	
SUBGROUP 2	xxx					
Control Group, n(%)	xxx (xx.x)	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	x xx
Intervention Group, n(%)	xxx (xx.x)	xxx x (x xx)	xxx.x	xxx.x, xxx x	xxx	
…						

[a]Eligible covariates were determined by demonstrating a statiststically significant association, at the 0.05 level, with CCQ Total Score in an ANCOVA model. Candidate covariates for the ANCOVA model were the significant covariates from the Adherent Symbicort Sensitivity analysis (Table 11.2.1). T-test p-values are reported, * indicates the Satterthwaite t-static is reported. SD: Standard Deviation.

Table 18.1.2 CCQ Total Score Sub-Group Analyses[a]: Per-Protocol Analysis Set
Use same format as Table 18.1.1. For every covariate found to be significant in the CCQ Total Score ANCOVA model presented in Table 17.2 will then be included in the below subgroup analyses. If any continuous covariate is found to be significant by the secondary outcome ANCOVA model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available. *Note: footnote will call out Table 11.2.2, instead*

Table 18.2.1 CCQ Symptom Domain Score Sub-Group Analyses[a]: Full Analysis Set
For every covariate found to be significant in the CCQ Symptom Domain Score ANCOVA model presented in Table 17.1 will then be included in the subgroup analyses. If any continuous covariate is found to be significant by the secondary outcome ANCOVA model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available. This table will use the same format as Table 18.1.1.

Table 18.2.2 CCQ Symptom Domain Score Sub-Group Analyses[a]: Per-Protocol Analysis Set
For every covariate found to be significant in the CCQ Symptom Domain Score ANCOVA model presented in Table 17.2 will then be included in the subgroup analyses. If any continuous covariate is found to be significant by the secondary outcome ANCOVA model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available. This table will use the same format as Table 18.1.1. *Note: footnote will call out Table 11.2.2, instead*

Table 18.3.1 CCQ Functional Domain Score Sub-Group Analyses[a]: Full Analysis Set
Use same format as Table 18.1.1. For every covariate found to be significant in the CCQ Functional Domain Score ANCOVA model presented in Table 17.1 will then be included in the below subgroup analyses. If any continuous covariate is found to be significant by the secondary outcome ANCOVA model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available.

Table 18.3.2 CCQ Functional Domain Score Sub-Group Analyses[a]: Per-Protocol Analysis Set
Use same format as Table 18.1.1. For every covariate found to be significant in the CCQ Functional Domain Score ANCOVA model presented in Table 17.2 will then be included in the below subgroup analyses. If any continuous covariate is found to be significant by the secondary outcome ANCOVA model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available. *Note: footnote will call out Table 11.2.2, instead*

Table 18.4.1 CCQ Mental Domain Score Sub-Group Analyses[a]: Full Analysis Set
Use same format as Table 18.1.1. For every covariate found to be significant in the CCQ Mental Domain Score ANCOVA model presented in Table 17.1 will then be included in the below subgroup analyses. If any continuous covariate is found to be significant by the secondary outcome ANCOVA model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available.

Table 18.4.2 CCQ Mental Domain Score Sub-Group Analyses[a]: Per-Protocol Analysis Set
Use same format as Table 18.1.1. For every covariate found to be significant in the CCQ Mental Domain Score ANCOVA model presented in Table 17.2 will then be included in the below subgroup analyses. If any continuous covariate is found to be significant by the secondary outcome ANCOVA model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available. *Note: footnote will call out Table 11.2.2, instead*

Table 19. Association Between Adherent Days[a] and Change From Baseline in CCQ Total and Domain Scores by Analysis Population

	Number of Adherent Days			
	FAS Population (N=XXX)		PP Population N=(XXX)	
	Pearson Correlation	P-value	Pearson Correlation	P-value
CONTROL GROUP				
CCQ Total Score	x xxx	x xxx	x xxx	x xxx
CCQ Symptom Domain Score	x xxx	x xxx	x xxx	x xxx
CCQ Functional Domain Score	x xxx	x xxx	x xxx	x xxx
CCQ Mental Domain Score	x xxx	x xxx	x xxx	x xxx
INTERVENTION GROUP				
CCQ Total Score	x xxx	x xxx	x xxx	x xxx
CCQ Symptom Domain Score	x xxx	x xxx	x xxx	x xxx
CCQ Functional Domain Score	x xxx	x xxx	x xxx	x xxx
CCQ Mental Domain Score	x xxx	x xxx	x xxx	x xxx

[a]Adherent days is the number of study days a subject took exactly two sets of two puffs of their Symbicort medication.

Table 20.1 Change From Baseline in CCQ Total and Domain Scores ANCOVA Model Results: Full Analysis Set

	CCQ Total Change Score[a] (N=XXX)		CCQ Symptom Change Score[a] (N=XXX)		CCQ Functional State Change Score[a] (N=XXX)		CCQ Mental State Change Score[a] (N=XXX)	
Covariate	Mean (95% CI)	P-value	Mean (95% CI)	P-value	Mean (95% CI)	P-value	Mean (95% CI)	P-value
Age at Enrollment	xxx x (xxx.x, xxx x)	x.xx	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx x, xxx x)	x.xx	xxx.x (xxx x, xxx.x)	x xx
Race								
White	xxx x (xxx.x, xxx x)	x.xx	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx x, xxx x)	x.xx	xxx.x (xxx x, xxx.x)	x xx
Non-White	xxx x (xxx.x, xxx x)	x.xx	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx x, xxx x)	x.xx	xxx.x (xxx x, xxx.x)	x xx
Sex								
Male	xxx x (xxx.x, xxx x)	x.xx	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx x, xxx x)	x.xx	xxx.x (xxx x, xxx.x)	x xx
Female	xxx x (xxx.x, xxx x)	x.xx	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx x, xxx x)	x.xx	xxx.x (xxx x, xxx.x)	x xx
Smoking Status								
Current	xxx x (xxx.x, xxx x)	x.xx	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx x, xxx x)	x.xx	xxx.x (xxx x, xxx.x)	x xx
Former	xxx x (xxx.x, xxx x)	x.xx	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx x, xxx x)	x.xx	xxx.x (xxx x, xxx.x)	x xx
Number of COPD Exacerbations	xxx x (xxx.x, xxx x)	x.xx	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx x, xxx x)	x.xx	xxx.x (xxx x, xxx.x)	x xx

Covariate	CCQ Total Change Score[a] (N=XXX) Mean (95% CI)	P-value	CCQ Symptom Change Score[a] (N=XXX) Mean (95% CI)	P-value	CCQ Functional State Change Score[a] (N=XXX) Mean (95% CI)	P-value	CCQ Mental State Change Score[a] (N=XXX) Mean (95% CI)	P-value
COPD Exacerbation Severity								
Moderate	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx.x, xxx.x)	x xx	xxx.x (xxx x, xxx x)	x xx	xxx x (xxx.x, xxx.x)	x xx
Severe/Very Severe	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx.x, xxx.x)	x xx	xxx.x (xxx x, xxx x)	x xx	xxx x (xxx.x, xxx.x)	x xx
Prior Symbicort Treatment								
Symbicort Naive	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx.x, xxx.x)	x xx	xxx.x (xxx x, xxx x)	x xx	xxx x (xxx.x, xxx.x)	x xx
Symbicort Pre-treated	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx.x, xxx.x)	x xx	xxx.x (xxx x, xxx x)	x xx	xxx x (xxx.x, xxx.x)	x xx
Time (months) on ICS/LABA Medication at Baseline								
Less than Six Months	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx.x, xxx.x)	x xx	xxx.x (xxx x, xxx x)	x xx	xxx x (xxx.x, xxx.x)	x xx
Six or More Months	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx.x, xxx.x)	x xx	xxx.x (xxx x, xxx x)	x xx	xxx x (xxx.x, xxx.x)	x xx
Group								
Control	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx.x, xxx.x)	x xx	xxx.x (xxx x, xxx x)	x xx	xxx x (xxx.x, xxx.x)	x xx
Intervention	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx.x, xxx.x)	x xx	xxx.x (xxx x, xxx x)	x xx	xxx x (xxx.x, xxx.x)	x xx
Device Time	xxx x (xxx x, xxx.x)	x xx	xxx x (xxx.x, xxx.x)	x xx	xxx.x (xxx x, xxx x)	x xx	xxx x (xxx.x, xxx.x)	x xx

ANCOVA model based means are reported, Candidate covariates for the ANCOVA model were the significant covariates from the Adherent Symbicort Sensitivity analysis (Table 11.2.1). CCQ: Clinical COPD Questionnaire, CI: Confidence Interval, EOT:End of Treatment Visit.

[a]Change scores are calculated as Baseline score – EOT score. Baseline is the date randomization occurred; End of treatment is the latest date among assessments completed around the date the final phone/device was returned. CCQ Scores range from 0 – 6, with higher values indicative of poorer health status. COPD Severity Level: Moderate is FEV1 % predicted 50 – 79%, Severe/Very Severe is FEV1 % predicted < 50%.

Table 20.2 Change From Baseline in CCQ Total and Domain Scores ANCOVA Model Results: Per-Protocol Analysis Set

Use same format as Table 20.1, but using PP. *Note: footnote will call out Table 11.2.2, instead*

Table 21.1.1 Change From Baseline in CCQ Total Score Sub-Group Analyses: Full Analysis Set
For every covariate found to be significant in the CCQ Total Score ANCOVA model presented in Table 20.1 will then be included in the subgroup analyses. If any continuous covariate is found to be significant by the secondary outcome ANCOVA model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available. This table will use the same format as Table 18.1.1.

Table 21.1.2 Change From Baseline in CCQ Total Score Sub-Group Analyses: Per-Protocol Analysis Set
For every covariate found to be significant in the CCQ Total Score ANCOVA model presented in Table 20.2 will then be included in the subgroup analyses. If any continuous covariate is found to be significant by the secondary outcome ANCOVA model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available. This table will use the same format as Table 18.1.1.

Table 21.2.1 Change From Baseline in CCQ Symptom Domain Score Sub-Group Analyses: Full Analysis Set
For every covariate found to be significant in the CCQ Symptom Domain Score ANCOVA model presented in Table 20.1 will then be included in the subgroup analyses. If any continuous covariate is found to be significant by the secondary outcome ANCOVA model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available. This table will use the same format as Table 18.1.1.

Table 21.2.2 Change From Baseline in CCQ Symptom Domain Score Sub-Group Analyses: Per-Protocol Analysis Set
For every covariate found to be significant in the CCQ Symptom Domain Score ANCOVA model presented in Table 20.2 will then be included in the subgroup analyses. If any continuous covariate is found to be significant by the secondary outcome ANCOVA model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available. This table will use the same format as Table 18.1.1.

Table 21.3.1 Change From Baseline in CCQ Functional Domain Score Sub-Group Analyses: Full Analysis Set
For every covariate found to be significant in the CCQ Functional Domain Score ANCOVA model presented in Table 20.1 will then be included in the subgroup analyses. If any continuous covariate is found to be significant by the secondary outcome ANCOVA model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available. This table will use the same format as Table 18.1.1.

Table 21.3.2 Change From Baseline in CCQ Functional Domain Score Sub-Group Analyses: Per-Protocol Analysis Set
For every covariate found to be significant in the CCQ Functional Domain Score ANCOVA model presented in Table 20.2 will then be included in the subgroup analyses. If any continuous covariate is found to be significant by the secondary outcome ANCOVA model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available. This table will use the same format as Table 18.1.1.

Table 21.4.1 Change From Baseline in CCQ Mental Domain Score Sub-Group Analyses: Full Analysis Set
For every covariate found to be significant in the CCQ Mental Domain Score ANCOVA model presented in Table 20.1 will then be included in the subgroup analyses. If any continuous covariate is found to be significant by the secondary outcome ANCOVA model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available. This table will use the same format as Table 18.1.1.

Table 21.4.2 Change From Baseline in CCQ Mental Domain Score Sub-Group Analyses: Per-Protocol Analysis Set
For every covariate found to be significant in the CCQ Mental Domain Score ANCOVA model presented in Table 20.2 will then be included in the subgroup analyses. If any continuous covariate is found to be significant by the secondary outcome ANCOVA model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available. This table will use the same format as Table 18.1.1.

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Table 22.1 Weekly CCQ Total Score by Study Interval – Intervention Group: Full Analysis Set

	Intervention Group (N=XXX)	N	Responders[a] n, (%)	Mean (SD)	Median	Range
Interval 1						
Week 1	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x
Week 2	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x
Week 3	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x
Week 4	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x
Week 5	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x
Week 6	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x
Week 7	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x
Week 8	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x
Week 9	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x
Overall	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x
Interval 2						
Week 10	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x
Week 11	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x
Week 12	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x
Week 13	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x
Week 14	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x
Week 15	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x
Week 16	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x
Week 17	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x
Week 18	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x
Overall	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x

	Intervention Group (N=XXX)	N	Responders[a] n, (%)	Mean (SD)	Median	Range
Interval 3						
Week 19	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x
Week 20	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x
Week 21	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x
Week 22	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x
Week 23	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x
Week 24	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x
Week 25	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x
Week 26	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x
Overall	xxx	xxx	xxx (xx x)	xxx x (x.xx)	xxx.x	xxx.x, xxx x

SD: Standard Deviation, CCQ: Clinical COPD Questionnaire, EOT: End of Treatment; CCQ Scores range from 0 – 6, with higher values indicative or poorer health status; Interval 1: From study day 1 to study day 63 (inclusive); Interval 2: Study day 64 to study day 126 (inclusive); Interval 3: Study day 127 to EOT (inclusive).
[a]A responder is a subject who experienced a decrease of at least 0.4 units from the Baseline CCQ Total score.

Table 22.2 Weekly CCQ Total Score by Study Interval – Intervention Group: Per-Protocol Analysis Set
Use same format as Table 22.1, but with PP

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Table 23.1 Weekly CCQ Total Score by Study Interval ANCOVA Model Results– Intervention Group: Full Analysis Set

	Interval 1 to Interval 2 (N=XXX)		Interval 2 to Interval 3 (N=XXX)		Interval 1 to Interval 3 (N=XXX)	
Covariate	Mean Weekly CCQ Total Score (95% CI)	P-value	MeanWeekly CCQ Total Score (95% CI)	P-value	Mean Weekly Total CCQ Score (95% CI)	P-value
Age at Enrollment	xxx x (xxx x, xxx x)	x.xx	xxx.x (xxx x, xxx.x)	x xx	xxx x (xxx x, xxx.x)	x xx
Race						
White	xxx x (xxx x, xxx x)	x.xx	xxx.x (xxx x, xxx.x)	x xx	xxx x (xxx x, xxx.x)	x xx
Non-White	xxx x (xxx x, xxx x)	x.xx	xxx.x (xxx x, xxx.x)	x xx	xxx x (xxx x, xxx.x)	x xx
Sex						
Male	xxx x (xxx x, xxx x)	x.xx	xxx.x (xxx x, xxx.x)	x xx	xxx x (xxx x, xxx.x)	x xx
Female	xxx x (xxx x, xxx x)	x.xx	xxx.x (xxx x, xxx.x)	x xx	xxx x (xxx x, xxx.x)	x xx
COPD Exacerbation Severity						
Moderate	xxx x (xxx x, xxx x)	x.xx	xxx.x (xxx x, xxx.x)	x xx	xxx x (xxx x, xxx.x)	x xx
Severe/Very Severe	xxx x (xxx x, xxx x)	x.xx	xxx.x (xxx x, xxx.x)	x xx	xxx x (xxx x, xxx.x)	x xx
Number of COPD Exacerbations	xxx x (xxx x, xxx x)	x.xx	xxx.x (xxx x, xxx.x)	x xx	xxx x (xxx x, xxx.x)	x xx

Covariate	Interval 1 to Interval 2 (N=XXX) Mean Weekly CCQ Total Score (95% CI)	P-value	Interval 2 to Interval 3 (N=XXX) MeanWeekly CCQ Total Score (95% CI)	P-value	Interval 1 to Interval 3 (N=XXX) Mean Weekly Total CCQ Score (95% CI)	P-value
Smoking Status						
Current	xxx x (xxx x, xxx x)	x xx	xxx.x (xxx x, xxx.x)	x xx	xxx x (xxx.x, xxx x)	x xx
Former	xxx x (xxx x, xxx x)	x xx	xxx.x (xxx x, xxx.x)	x xx	xxx x (xxx.x, xxx.x)	x xx
Prior Symbicort Treatment						
Symbicort Naïve	xxx x (xxx x, xxx x)	x xx	xxx.x (xxx x, xxx.x)	x xx	xxx x (xxx.x, xxx x)	x xx
Symbicort Pre-treated	xxx x (xxx x, xxx x)	x xx	xxx.x (xxx x, xxx.x)	x xx	xxx x (xxx.x, xxx x)	x xx
Time (months) on ICS/LABA Medication at Baseline						
Less than Six Months	xxx x (xxx x, xxx x)	x xx	xxx.x (xxx x, xxx.x)	x xx	xxx x (xxx.x, xxx x)	x xx
Six or More Months	xxx x (xxx x, xxx x)	x xx	xxx.x (xxx x, xxx.x)	x xx	xxx x (xxx.x, xxx x)	x xx
Device Time	xxx x (xxx x, xxx x)	x xx	xxx.x (xxx x, xxx.x)	x xx	xxx x (xxx.x, xxx x)	x xx

ANCOVA model based means are reported, Candidate covariates for the ANCOVA model were the significant covariates from the Adherent Symbicort Sensitivity analysis (Table 11.2.1). CCQ: Clinical COPD Questionnaire, CI: Confidence Interval, EOT: End of Treatment. Interval 1: From study day 1 to study day 63 (inclusive); Interval 2: Study day 64 to study day 126 (inclusive); Interval 3: Study day 127 to EOT (inclusive). CCQ Scores range from 0 – 6, with higher values indicative of poorer health status. COPD Severity Level: Moderate is FEV1 % predicted 50 – 79%, Severe/Very severe is FEV1 % predicted < 50%.

Table 23.2 Weekly CCQ Total Score by Study Interval ANCOVA Model Results– Intervention Group: Per-Protocol Analysis Set

Use same format as Table 23.1, but using PP. *Note: footnote will call out Table 11.2.2, instead*

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Table 24.1 Weekly CCQ Domain Scores by Study Interval – Intervention Group: Full Analysis Set

	Intervention Group (N=XXX)	N	Mean (SD)	Median	Range
Symptom Score					
Interval 1					
Week 1	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 2	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 3	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 4	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 5	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 6	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 7	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 8	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 9	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Overall	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Interval 2					
Week 10	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 11	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 12	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 13	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 14	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 15	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 16	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 17	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 18	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Overall	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x

	Intervention Group (N=XXX)	N	Mean (SD)	Median	Range
Interval 3					
Week 19	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 20	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 21	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 22	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 23	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 24	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 25	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 26	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Overall	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Functional State Score					
Interval 1	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 1	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 2	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 3	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 4	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 5	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 6	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 7	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 8	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 9	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Overall	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x

	Intervention Group (N=XXX)	N	Mean (SD)	Median	Range
Interval 2					
Week 10	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 11	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 12	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 13	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 14	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 15	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 16	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 17	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 18	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Overall	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Interval 3					
Week 19	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 20	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 21	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 22	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 23	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 24	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 25	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 26	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Overall	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x

	Intervention Group (N=XXX)	N	Mean (SD)	Median	Range
Mental State Score					
Interval 1					
Week 1	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 2	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 3	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 4	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 5	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 6	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 7	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 8	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 9	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Overall	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Interval 2					
Week 10	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 11	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 12	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 13	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 14	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 15	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 16	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 17	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Week 18	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x
Overall	xxx	xxx	xxx.x (x xx)	xxx x	xxx x, xxx x

	Intervention Group (N=XXX)	N	Mean (SD)	Median	Range
Interval 3					
Week 19	xxx	xxx	xxx x (x xx)	xxx x	xxx x, xxx x
Week 20	xxx	xxx	xxx x (x xx)	xxx x	xxx x, xxx x
Week 21	xxx	xxx	xxx x (x xx)	xxx x	xxx x, xxx x
Week 22	xxx	xxx	xxx x (x xx)	xxx x	xxx x, xxx x
Week 23	xxx	xxx	xxx x (x xx)	xxx x	xxx x, xxx x
Week 24	xxx	xxx	xxx x (x xx)	xxx x	xxx x, xxx x
Week 25	xxx	xxx	xxx x (x xx)	xxx x	xxx x, xxx x
Week 26	xxx	xxx	xxx x (x xx)	xxx x	xxx x, xxx x
Overall	xxx	xxx	xxx x (x xx)	xxx x	xxx x, xxx x

SD: Standard Deviation, CCQ: Clinical COPD Questionnaire, EOT: End of Treatment. CCQ Scores range from 0 – 6, with higher values indicative or poorer health status.
Interval 1: From study day 1 to study day 63 (inclusive); Interval 2: Study day 64 to study day 126 (inclusive); Interval 3: Study day 127 to EOT (inclusive).

Table 24.2 Weekly CCQ Domain Scores by Study Interval – Intervention Group: Per-Protocol Analysis Set
Use same format as Table 24.1, but with PP

Table 25.1.1 Weekly CCQ Symptom Score by Study Interval ANCOVA Model Results– Intervention Group: Full Analysis Set
Use same format as Table 23.1, but using CCQ Symptom Score.

Table 25.1.2 Weekly CCQ Symptom Score by Study Interval ANCOVA Model Results– Intervention Group: Per-Protocol Analysis Set
Use same format as Table 23.2, but using CCQ Symptom Score. *Note: footnote will call out Table 11.2.2, instead*

Table 25.2.1 Weekly CCQ Functional Score by Study Interval ANCOVA Model Results– Intervention Group: Full Analysis Set
Use same format as Table 23.1, but using the CCQ Functional Score.

Table 25.2.2 Weekly CCQ Functional Score by Study Interval ANCOVA Model Results– Intervention Group: Per-Protocol Analysis Set
Use same format as Table 23.2, but using CCQ Functional Score. *Note: footnote will call out Table 11.2.2, instead*

Table 25.3.1 Weekly CCQ Mental Score by Study Interval ANCOVA Model Results– Intervention Group: Full Analysis Set
Use same format as Table 23.1, but using CCQ Mental Score.

Table 25.3.2 Weekly CCQ Mental Score by Study Interval ANCOVA Model Results– Intervention Group: Per-Protocol Analysis Set
Use same format as Table 23.2, but using CCQ Mental Score. *Note: footnote will call out Table 11.2.2, instead*

Table 26.1 Average Number of Sets of Adherent Symbicort Puffs[a] per Day During Each Study Interval: Full Analysis Set

	Control Group (N=XXX)	Intervention Group (N=XXX)	Total (N=XXX)
Interval 1			
n	xxx	xxx	xxx
Mean (SD)	xxx x (x xx)	xxx x (x xx)	xxx x (x.xx)
Median	xxx x	xxx x	xxx x
Range	xxx x, xxx.x	xxx.x, xxx x	xxx.x, xxx x
Missing	xxx	xxx	xxx
Interval 2			
n	xxx	xxx	xxx
Mean (SD)	xxx x (x xx)	xxx x (x xx)	xxx x (x.xx)
Median	xxx x	xxx x	xxx x
Range	xxx x, xxx.x	xxx.x, xxx x	xxx.x, xxx x
Missing	xxx	xxx	xxx
Interval 3			
n	xxx	xxx	xxx
Mean (SD)	xxx x (x xx)	xxx x (x xx)	xxx x (x.xx)
Median	xxx x	xxx x	xxx x
Range	xxx x, xxx.x	xxx.x, xxx x	xxx.x, xxx x
Missing	xxx	xxx	xxx

SD: Standard Deviation, EOT: End of Treatment.
[a]A set is two puffs taken on the same calendar day, with the two puffs taken within 60 minutes of each other.. Interval 1: From study day 1 to study day 63 (inclusive); Interval 2: Study day 64 to study day 126 (inclusive); Interval 3: Study day 127 to EOT (inclusive).

Table 26.2 Average Number of Sets of Adherent Symbicort Puffs[a] per Day During Each Study Interval: Per-Protocol Analysis Set

Use the same format as Table 26.1, but with PP

Table 26.3 Average Number of Symbicort Inhalations per Day During Each Study Interval: Full Analysis Set

	Control Group (N=XXX)	Intervention Group (N=XXX)	Total (N=XXX)
Interval 1			
n	xxx	xxx	xxx
Mean (SD)	xxx x (x xx)	xxx x (x xx)	xxx x (x.xx)
Median	xxx x	xxx x	xxx x
Range	xxx x, xxx.x	xxx.x, xxx x	xxx.x, xxx x
Missing	xxx	xxx	xxx
Interval 2			
n	xxx	xxx	xxx
Mean (SD)	xxx x (x xx)	xxx x (x xx)	xxx x (x.xx)
Median	xxx x	xxx x	xxx x
Range	xxx x, xxx.x	xxx.x, xxx x	xxx.x, xxx x
Missing	xxx	xxx	xxx
Interval 3			
n	xxx	xxx	xxx
Mean (SD)	xxx x (x xx)	xxx x (x xx)	xxx x (x.xx)
Median	xxx x	xxx x	xxx x
Range	xxx x, xxx.x	xxx.x, xxx x	xxx.x, xxx x
Missing	xxx	xxx	xxx

SD: Standard Deviation, EOT: End of Treatment.
A set is two puffs taken on the same calendar day, with the two puffs taken within 60 minutes of each other.. Interval 1: From study day 1 to study day 63 (inclusive); Interval 2: Study day 64 to study day 126 (inclusive); Interval 3: Study day 127 to EOT (inclusive).

Table 26.4 Average Number of Symbicort Inhalations per Day During Each Study Interval: Per-Protocol Analysis Set
Use the same format as Table 26.3, but with PP

Table 26.5 Average Number of Complete Sets of Symbicort Puffs per Day During Each Study Interval: Full Analysis Set

	Control Group (N=XXX)	Intervention Group (N=XXX)	Total (N=XXX)
Interval 1			
n	xxx	xxx	xxx
Mean (SD)	xxx x (x xx)	xxx x (x xx)	xxx x (x.xx)
Median	xxx x	xxx x	xxx x
Range	xxx x, xxx.x	xxx.x, xxx x	xxx.x, xxx x
Missing	xxx	xxx	xxx
Interval 2			
n	xxx	xxx	xxx
Mean (SD)	xxx x (x xx)	xxx x (x xx)	xxx x (x.xx)
Median	xxx x	xxx x	xxx x
Range	xxx x, xxx.x	xxx.x, xxx x	xxx.x, xxx x
Missing	xxx	xxx	xxx
Interval 3			
n	xxx	xxx	xxx
Mean (SD)	xxx x (x xx)	xxx x (x xx)	xxx x (x.xx)
Median	xxx x	xxx x	xxx x
Range	xxx x, xxx.x	xxx.x, xxx x	xxx.x, xxx x
Missing	xxx	xxx	xxx

SD: Standard Deviation, EOT: End of Treatment. A complete set is two puffs taken on the same calendar day, with the two puffs taken within 60 minutes of each other. Interval 1: From study day 1 to study day 63 (inclusive); Interval 2: Study day 64 to study day 126 (inclusive); Interval 3: Study day 127 to EOT (inclusive).

Table 26.6 Average Number of Complete Sets of Symbicort Puffs per Day During Each Study Interval: Per-Protocol Analysis Set

Use the same format as Table 26.5, but with PP

Table 27.1 Average Number of Sets of Adherent Symbicort Puffs per Day During Each Study Interval ANCOVA Model Results: Full Analysis Set

Covariate	FAS Population (N=XXX) Mean Sets of Symbicort Puffs/Day (95% CI)	P-value
Age at Enrollment	xxx x (xxx x, xxx x)	x.xx
Race		
White	xxx x (xxx x, xxx x)	x.xx
Non-White	xxx x (xxx x, xxx x)	x.xx
Sex		
Male	xxx x (xxx x, xxx x)	x.xx
Female	xxx x (xxx x, xxx x)	x.xx
Smoking Status		
Current	xxx x (xxx x, xxx x)	x.xx
Former	xxx x (xxx x, xxx x)	x.xx
Number of COPD Exacerbations	xxx x (xxx x, xxx x)	x.xx

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Covariate	FAS Population (N=XXX) Mean Sets of Symbicort Puffs/Day (95% CI)	P-value
COPD Exacerbation Severity		
Moderate	xxx x (xxx x, xxx x)	x.xx
Severe/Very Severe	xxx x (xxx x, xxx x)	x.xx
Prior Symbicort Treatment		
Symbicort Naïve	xxx x (xxx x, xxx x)	x.xx
Symbicort Pre-treated	xxx x (xxx x, xxx x)	x.xx
Time (months) on ICS/LABA Medication at Baseline		
Less than Six Months	xxx x (xxx x, xxx x)	x.xx
Six or More Months	xxx x (xxx x, xxx x)	x.xx
Group		
Control	xxx x (xxx x, xxx x)	x.xx
Intervention	xxx x (xxx x, xxx x)	x.xx
Study Interval		
Interval 1	xxx x (xxx x, xxx x)	x.xx
Interval 2	xxx x (xxx x, xxx x)	x.xx
Interval 3	xxx x (xxx x, xxx x)	x.xx

Covariate	FAS Population (N=XXX) Mean Sets of Symbicort Puffs/Day (95% CI)	P-value
Study Interval*Group	xxx.x (xxx x, xxx.x)	x.xx
Device Time	xxx.x (xxx x, xxx.x)	x.xx

ANCOVA model based means are reported Candidate covariates for the ANCOVA model were the significant covariates from the Adherent Symbicort Sensitivity analysis (Table 11.2.1). CI: Confidence Interval, EOT: End of Treatment. COPD Severity Level: Moderate is FEV1 % predicted 50 – 79%, Severe/Very Severe is FEV1 % predicted < 50%. Interval 1: From study day 1 to study day 63 (inclusive); Interval 2: Study day 64 to study day 126 (inclusive); Interval 3: Study day 127 to EOT (inclusive).

Table 27.2 Average Number of Sets of Adherent Symbicort Puffs per Day During Each Study Interval ANCOVA Model Results: Per-Protocol Analysis Set

Use the same format as Table 27.1, but using PP. *Note: footnote will call out Table 11.2.2, instead*

Table 28.1 Average Number of Sets of Adherent Symbicort Puffs per Day During Each Study Interval Sub-Group Analyses: Full Analysis Set

For every covariate found to be significant in the ANCOVA model presented in Table 27.1 will then be included in the subgroup analyses. If any continuous covariate is found to be significant by the secondary outcome ANCOVA model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available. This table will use the same format as Table 18.1.1.

Table 28.2 Average Number of Sets of Adherent Symbicort Puffs per Day During Each Study Interval Sub-Group Analyses: Per-Protocol Analysis Set

For every covariate found to be significant in the ANCOVA model presented in Table 27.2 will then be included in the subgroup analyses. If any continuous covariate is found to be significant by the secondary outcome ANCOVA model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available. This table will use the same format as Table 18.1.1.

Table 29.1 Average Number of Sets of Adherent Symbicort Puffs per Day during Each Study Interval ANCOVA Model Results, Stratified by Group: Full Analysis Set

	Control Group Only (N=XXX)		Intervention Group Only (N=XXX)	
Covariate	Mean Sets of Symbicort Puffs/Day (95% CI)	P-value	Mean Sets of Symbicort Puffs/Day (95% CI)	P-value
Age at Enrollment	xxx x (xxx x, xxx x)	x xx	xxx x (xxx.x, xxx.x)	x xx
Race				
White	xxx x (xxx x, xxx x)	x xx	xxx x (xxx.x, xxx.x)	x xx
Non-White	xxx x (xxx x, xxx x)	x xx	xxx x (xxx.x, xxx.x)	x xx
Sex				
Male	xxx x (xxx x, xxx x)	x xx	xxx x (xxx x, xxx.x)	x xx
Female	xxx x (xxx x, xxx x)	x xx	xxx x (xxx.x, xxx.x)	x xx
Study Interval				
Interval 1	xxx x (xxx x, xxx x)	x xx	xxx x (xxx.x, xxx.x)	x xx
Interval 2	xxx x (xxx x, xxx x)	x xx	xxx x (xxx.x, xxx.x)	x xx
Interval 3	xxx x (xxx x, xxx x)	x xx	xxx x (xxx.x, xxx.x)	x xx

Covariate	Control Group Only (N=XXX) Mean Sets of Symbicort Puffs/Day (95% CI)	P-value	Intervention Group Only (N=XXX) Mean Sets of Symbicort Puffs/Day (95% CI)	P-value
Smoking Status				
Current	xxx x (xxx x, xxx.x)	x xx	xxx.x (xxx x, xxx.x)	x xx
Former	xxx x (xxx x, xxx.x)	x xx	xxx.x (xxx x, xxx.x)	x xx
Number of COPD Exacerbations	xxx x (xxx x, xxx.x)	x xx	xxx.x (xxx x, xxx.x)	x xx
COPD Exacerbation Severity				
Moderate	xxx x (xxx x, xxx.x)	x xx	xxx.x (xxx x, xxx.x)	x xx
Severe/Very Severe	xxx x (xxx x, xxx.x)	x xx	xxx.x (xxx x, xxx.x)	x xx
Prior Symbicort Treatment				
Symbicort Naïve	xxx x (xxx x, xxx.x)	x xx	xxx.x (xxx x, xxx.x)	x xx
Symbicort Pre-treated	xxx x (xxx x, xxx.x)	x xx	xxx.x (xxx x, xxx.x)	x xx
Time (months) on ICS/LABA Medication at Baseline				
Less than Six Months	xxx x (xxx x, xxx.x)	x xx	xxx.x (xxx x, xxx.x)	x xx
Six or More Months	xxx x (xxx x, xxx.x)	x xx	xxx.x (xxx x, xxx.x)	x xx
Device Time	xxx x (xxx x, xxx.x)	x xx	xxx.x (xxx x, xxx.x)	x xx

ANCOVA model based means are reported, Candidate covariates for the ANCOVA model were the significant covariates from the Adherent Symbicort Sensitivity analysis (Table 11.2.1). CI: Confidence Interval, EOT: End of Treatment. COPD Severity Level: Moderate is FEV1 % predicted 50 – 79%, Severe/Very severe is FEV1 % predicted < 50%. Interval 1: From study day 1 to study day 63 (inclusive); Interval 2: Study day 64 to study day 126 (inclusive); Interval 3: Study day 127 to EOT (inclusive).

Table 29.2 Average Number of Sets of Adherent Symbicort Puffs per Day at Each Study Interval ANCOVA Model Results, Stratified by Group: Per-Protocol Analysis Set

Use the same format as Table 29.1, but using PP . *Note: footnote will call out Table 11.2.2, instead*

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Table 30.1 Summary of Adherent Use: Full Analysis Set

	Control Group (N=XXX)	Intervention Group (N=XXX)	Total (N=XXX)	P-value
Adherent Days[a]				
n	xxx	xxx	xxx	x xx*
Mean (SD)	xxx x (x xx)	xxx x (x xx)	xxx x (x xx)	
Median	xxx x	xxx x	xxx x	
Range	xxx.x, xxx x	xxx x, xxx x	xxx x, xxx x	
Missing	xxx	xxx	xxx	
Proportion of Adherent Days[a]				
n	xxx	xxx	xxx	x xx
Mean (SD)	xxx x (x xx)	xxx x (x xx)	xxx x (x xx)	
Median	xxx x	xxx x	xxx x	
Range	xxx.x, xxx x	xxx x, xxx x	xxx x, xxx x	
Missing	xxx	xxx	xxx	
Percent Adherent[b]				x xxx
n	xxx	xxx	xxx	
Less than 80%	xxx (xx x)	xxx (xx x)	xxx (xx x)	
80% or More	xxx (xx x)	xxx (xx x)	xxx (xx x)	
Missing	xxx	xxx	xxx	
No Use Days[c]				
n	xxx	xxx	xxx	x xx
Mean (SD)	xxx x (x xx)	xxx x (x xx)	xxx x (x xx)	
Median	xxx x	xxx x	xxx x	
Range	xxx.x, xxx x	xxx x, xxx x	xxx x, xxx x	
Missing	xxx	xxx	xxx	

	Control Group (N=XXX)	Intervention Group (N=XXX)	Total (N=XXX)	P-value
Proportion of No Use Days[c]				
n	xxx	xxx	xxx	
Mean (SD)	xxx x (x xx)	xxx x (x xx)	xxx x (x xx)	x.xx*
Median	xxx x	xxx x	xxx x	
Range	xxx x, xxx x	xxx x, xxx x	xxx x, xxx x	
Missing	xxx	xxx	xxx	
Underuse Days[c]				
n	xxx	xxx	xxx	
Mean (SD)	xxx x (x xx)	xxx x (x xx)	xxx x (x xx)	x xx
Median	xxx x	xxx x	xxx x	
Range	xxx x, xxx x	xxx x, xxx x	xxx x, xxx x	
Missing	xxx	xxx	xxx	
Proportion of Underuse Days[d]				
n	xxx	xxx	xxx	
Mean (SD)	xxx.x (x xx)	xxx x (x xx)	xxx.x (x xx)	x xx
Median	xxx x	xxx x	xxx.x	
Range	xxx x, xxx x	xxx x, xxx.x	xxx x, xxx x	
Missing	xxx	xxx	xxx	

	Control Group (N=XXX)	Intervention Group (N=XXX)	Total (N=XXX)	P-value
Overuse Days[e]				
n	xxx	xxx	xxx	x xx*
Mean (SD)	xxx x (x xx)	xxx x (x xx)	xxx.x (x xx)	
Median	xxx x	xxx x	xxx.x	
Range	xxx.x, xxx x	xxx x, xxx x	xxx x, xxx x	
Missing	xxx	xxx	xxx	
Proportion of Overuse Days[e]				
n	xxx	xxx	xxx	x xx
Mean (SD)	xxx x (x xx)	xxx x (x xx)	xxx.x (x xx)	
Median	xxx x	xxx x	xxx.x	
Range	xxx.x, xxx x	xxx x, xxx x	xxx x, xxx x	
Missing	xxx	xxx	xxx	
Overuse Alert Days[f]				
n	xxx	xxx	xxx	x xx
Mean (SD)	xxx x (x xx)	xxx x (x xx)	xxx.x (x xx)	
Median	xxx x	xxx x	xxx.x	
Range	xxx.x, xxx x	xxx x, xxx x	xxx x, xxx x	
Missing	xxx	xxx	xxx	
Proportion of Overuse Alert Days[f]				
n	xxx	xxx	xxx	x xx
Mean (SD)	xxx x (x xx)	xxx x (x xx)	xxx.x (x xx)	
Median	xxx x	xxx x	xxx.x	
Range	xxx.x, xxx x	xxx x, xxx x	xxx x, xxx x	
Missing	xxx	xxx	xxx	

P-values are from a T-test or Chi-square for Percent Adherent. *Indicates the Satterthwaite t-static is reported. SD: Standard Deviation.

[a]Adherent days is the number of study days a subject is adherent with their Symbicort medication (exactly two sets of two puffs); [b]Percent Adherent is derived from proportion of adherent days; [c]No use days is the number of study days a subject took zero puffs of Symbicort a day; [d]Underuse days is the number of study days a subject took between one and three puffs of Symbicort a day; [e]Overuse days is the number of study days a subject took between five and 10 puffs of Symbicort a day; [f]Overuse alert days is the number of study days a subject took 11+ puffs of Symbicort a day.

Table 30.2 Summary Adherent Use: Per-Protocol Analysis Set

Use the same format as Table 30.1, but with PP

Table 31.1 Number of Adherent Days[a] ANCOVA Model Results: Full Analysis Set

Covariate	Number of Adherent Days (95% CI)	FAS Population (N=XXX) P-value
Age at Enrollment	xxx x (xxx x, xxx x)	x xx
Race		
White	xxx x (xxx x, xxx x)	x xx
Non-White	xxx x (xxx x, xxx x)	x xx
Sex		
Male	xxx x (xxx x, xxx x)	x xx
Female	xxx x (xxx x, xxx x)	x xx
Smoking Status		
Current	xxx x (xxx x, xxx x)	x xx
Former	xxx x (xxx x, xxx x)	x xx
Number of COPD Exacerbations	xxx x (xxx x, xxx x)	x xx

Covariate	Number of Adherent Days (95% CI)	FAS Population (N=XXX) P-value
COPD Exacerbation Severity		
Moderate	xxx x (xxx x, xxx x)	x xx
Severe/Very Severe	xxx x (xxx x, xxx x)	x xx
Prior Symbicort Treatment		
Symbicort Naïve	xxx x (xxx x, xxx x)	x xx
Symbicort Pre-treated	xxx x (xxx x, xxx x)	x xx
Time (months) on ICS/LABA Medication at Baseline		
Less than Six Months	xxx x (xxx x, xxx x)	x xx
Six or More Months	xxx x (xxx x, xxx x)	x xx
Group		
Control	xxx x (xxx x, xxx x)	x xx
Intervention	xxx x (xxx x, xxx x)	x xx
Device Time	xxx x (xxx x, xxx x)	x xx

[a]Adherent days is the number of study days a subject is adherent (exactly two sets of two puffs) with their Symbicort medication. ANCOVA model based means are reported, Candidate covariates for the ANCOVA model were the significant covariates from the Adherent Symbicort Sensitivity analysis (Table 11.2.1). CI: Confidence Interval. COPD Severity Level: Moderate is FEV1 % predicted 50 – 79%, Severe/Very Severe is FEV1 % predicted < 50%.

Table 31.2 Number of Adherent Days[a] ANCOVA Analyses: Per-Protocol Analysis Set
Use same format as Table 31.1, but using PP. *Note: footnote will call out Table 11.2.2, instead*

Table 32.1 Number of Adherent Days[a] Subgroup Analyses: Full Analysis Set
For every covariate found to be significant in the ANCOVA model presented in Table 31.1 will then be included in the subgroup analyses. If any continuous covariate is found to be significant by the secondary outcome ANCOVA model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available. This table will use the same format as Table 18.1.1.

Table 32.2 Number of Adherent Days[a] Subgroup Analyses: Per-Protocol Analysis Set
For every covariate found to be significant in the ANCOVA model presented in Table 31.2 will then be included in the subgroup analyses. If any continuous covariate is found to be significant by the secondary outcome ANCOVA model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available. This table will use the same format as Table 18.1.1.

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Table 33.1 Proportion of Adherent Days by Lung Function and Exacerbation Type at Baseline: Full Analysis Set

	Control Group (N=XXX)	Intervention Group (N=XXX)	Total (N=XXX)	P-value
PROPORTION OF ADHERENT DAYS[a]				
Lung Function at Baseline				
Better Lung Function at Baseline[b]				
N				
n	xxx	xxx	xxx	x xx*
Mean (SD)	xxx x (x xx)	xxx x (x xx)	xxx x (x xx)	
Median	xxx x	xxx x	xxx x	
Range	xxx.x, xxx x	xxx x, xxx x	xxx x, xxx x	
Missing	xxx	xxx	xxx	
Worse Lung Function at Baseline[c]				
n	xxx	xxx	xxx	x xx
Mean (SD)	xxx x (x xx)	xxx x (x xx)	xxx x (x xx)	
Median	xxx x	xxx x	xxx x	
Range	xxx.x, xxx x	xxx x, xxx x	xxx x, xxx x	
Missing	xxx	xxx	xxx	
Exacerbation Severity at Baseline				
Not Severe[d]				
n	xxx	xxx	xxx	x xx
Mean (SD)	xxx x (x xx)	xxx x (x xx)	xxx x (x xx)	
Median	xxx x	xxx x	xxx x	
Range	xxx.x, xxx x	xxx x, xxx x	xxx x, xxx x	
Missing	xxx	xxx	xxx	

	Control Group (N=XXX)	Intervention Group (N=XXX)	Total (N=XXX)	P-value
Severe[e]				
n	xxx	xxx	xxx	x xx*
Mean (SD)	xxx x (x xx)	xxx x (x xx)	xxx.x (x xx)	
Median	xxx x	xxx x	xxx.x	
Range	xxx.x, xxx x	xxx x, xxx x	xxx x, xxx x	
Missing	xxx	xxx	xxx	

T-test p-values are reported, *Indicates the Satterthwaite t-static is reported. SD: Standard Deviation.
[a]Adherent days is the number of study days a subject is adherent with their Symbicort medication (exactly two sets of two puffs); [b]A subject is considered to have better lung function at Baseline if they have Moderate COPD severity; [c]A subject is considered to have worse lung function at baseline if they have Severe/Very Severe COPD severity; [d]A subject is considered to have not severe exacerbation risk at Baseline if they experienced zero exacerbations or one exacerbation, not requiring hospitalization, within the past 12 months prior to Baseline; [e]A subject is considered to have severe exacerbation risk at Baseline if hospitalized for his most recent exacerbation or experienced two or more excerbations, regardless of hospitilization, within the past 12 months prior to Baseline.

Table 33.2 Proportion of Adherent Days by Lung Function at Baseline and Exacerbation Type at Baseline: Per-Protocol Analysis Set

Use the same format as Table 33.1, but with PP

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Table 34.1 Number of Symbicort Prescription Fills: Full Analysis Set

	Control Group (N=XXX)	Intervention Group (N=XXX)	Total (N=XXX)
Symbicort Prescriptions Written			
n	xxx	xxx	xxx
Mean (SD)	xxx x (x.xx)	xxx.x (x xx)	xxx x (x xx)
Median	xxx x	xxx.x	xxx x
Range	xxx.x, xxx x	xxx x, xxx x	xxx x, xxx.x
Symbicort Fills			
n	xxx	xxx	xxx
Mean (SD)	xxx x (x.xx)	xxx.x (x xx)	xxx x (x xx)
Median	xxx x	xxx.x	xxx x
Range	xxx.x, xxx x	xxx x, xxx x	xxx x, xxx.x
Missing	xxx	xxx	xxx
Symbicort Fills, Percent Expected			
n	xxx	xxx	xxx
Mean (SD)	xxx x (x.xx)	xxx.x (x xx)	xxx x (x xx)
Median	xxx x	xxx.x	xxx x
Range	xxx.x, xxx x	xxx x, xxx x	xxx x, xxx.x
Missing	xxx	xxx	xxx

SD: Standard Deviation

Table 34.2 Number of Symbicort Prescription Fills: Per-Protocol Analysis Set
Use the same format as Table 33.1, but with PP

Table 35.1 Number of Symbicort Prescription Fills ANCOVA Model Results: Full Analysis Set

Covariate	FAS Population (N=XXX) Number of Symbicort Prescription Fills (95% CI)	P-value
Age at Enrollment	xxx x (xxx x, xxx.x)	x xx
Race		
White	xxx x (xxx x, xxx.x)	x xx
Non-White	xxx x (xxx x, xxx.x)	x xx
Sex		
Male	xxx x (xxx x, xxx.x)	x xx
Female	xxx x (xxx x, xxx.x)	x xx
Smoking Status		
Current	xxx x (xxx x, xxx.x)	x xx
Former	xxx x (xxx x, xxx.x)	x xx
Number of COPD Exacerbations	xxx x (xxx x, xxx.x)	x xx

Covariate	FAS Population (N=XXX) Number of Symbicort Prescription Fills (95% CI)	P-value
COPD Exacerbation Severity		
Moderate	xxx x (xxx x, xxx.x)	x xx
Severe/Very Severe	xxx x (xxx x, xxx.x)	x xx
Prior Symbicort Treatment		
Symbicort Naïve	xxx x (xxx x, xxx.x)	x xx
Symbicort Pre-treated	xxx x (xxx x, xxx.x)	x xx
Time (months) on ICS/LABA Medication at Baseline		
Less than Six Months	xxx x (xxx x, xxx.x)	x xx
Six or More Months	xxx x (xxx x, xxx.x)	x xx
Group		
Control	xxx x (xxx x, xxx.x)	x xx
Intervention	xxx x (xxx x, xxx.x)	x xx
Device Time	xxx x (xxx x, xxx.x)	x xx

ANCOVA model based means are reported, Candidate covariates for the ANCOVA model were the significant covariates from the Adherent Symbicort Sensitivity analysis (Table 11.2.1). CI: Confidence Interval. COPD Severity Level: Moderate is FEV1 % predicted 50 – 79%, Severe/Very Severe is FEV1 % predicted < 50%.

Table 35.2 Number of Symbicort Prescription Fills ANCOVA Model Results: Per-Protcocol Analysis Set
Use the same format as Table 35.2, but using PP. *Note: footnote will call out Table 11.2.2, instead*

Table 36.1 Number of Symbicort Prescription Fills Sub-Group Analyses: Full Analysis Set
For every covariate found to be significant in the ANCOVA model presented in Table 35.1 will then be included in the subgroup analyses. If any continuous covariate is found to be significant by the secondary outcome ANCOVA model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available. This table will use the same format as Table 18.1.1.

Table 36.2 Number of Symbicort Prescription Fills Sub-Group Analyses: Per-Protcocol Analysis Set
For every covariate found to be significant in the ANCOVA model presented in Table 35.2 will then be included in the subgroup analyses. If any continuous covariate is found to be significant by the secondary outcome ANCOVA model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available. This table will use the same format as Table 18.1.1.

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Table 37.1 Number of No Use Days[a] ANCOVA Model Results: Full Analysis Set

Covariate	Number of No Use Days (95% CI)	FAS Population (N=XXX) P-value
Age at Enrollment	xxx x (xxx x, xxx x)	x xx
Race		
White	xxx x (xxx x, xxx x)	x xx
Non-White	xxx x (xxx x, xxx x)	x xx
Sex		
Male	xxx x (xxx x, xxx x)	x xx
Female	xxx x (xxx x, xxx x)	x xx
Smoking Status		
Current	xxx x (xxx x, xxx x)	x xx
Former	xxx x (xxx x, xxx x)	x xx
Number of COPD Exacerbations	xxx x (xxx x, xxx x)	x xx

Covariate	Number of No Use Days (95% CI)	FAS Population (N=XXX) P-value
COPD Exacerbation Severity		
Moderate	xxx x (xxx x, xxx x)	x xx
Severe/Very Severe	xxx x (xxx x, xxx x)	x xx
Prior Symbicort Treatment		
Symbicort Naïve	xxx x (xxx x, xxx x)	x xx
Symbicort Pre-treated	xxx x (xxx x, xxx x)	x xx
Time (months) on ICS/LABA Medication at Baseline		
Less than Six Months	xxx x (xxx x, xxx x)	x xx
Six or More Months	xxx x (xxx x, xxx x)	x xx
Group		
Control	xxx x (xxx x, xxx x)	x xx
Intervention	xxx x (xxx x, xxx x)	x xx
Device Time	xxx x (xxx x, xxx x)	x xx

[a]No Use days is the number of study days a subject takes zero inhalations of their Symbicort medication on a given day. ANCOVA model based means are reported, Candidate covariates for the ANCOVA model were the significant covariates from the Adherent Symbicort Sensitivity analysis (Table 11.2.1). CI: Confidence Interval. COPD Severity Level: Moderate is FEV1 % predicted 50 – 79%, Severe/Very Severe is FEV1 % predicted < 50%.

Table 37.2 Number of No Use Days[a] ANCOVA Analyses: Per-Protocol Analysis Set
Use same format as Table 37.1, but using PP. *Note: footnote will call out Table 11.2.2, instead*

Table 38.1 Number of No Use Days[a] Subgroup Analyses: Full Analysis Set
For every covariate found to be significant in the ANCOVA model presented in Table 37.1 will then be included in the subgroup analyses. If any continuous covariate is found to be significant by the secondary outcome ANCOVA model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available. This table will use the same format as Table 18.1.1.

Table 38.2 Number of No Use Days[a] Subgroup Analyses: Per-Protocol Analysis Set
For every covariate found to be significant in the ANCOVA model presented in Table 37.2 will then be included in the subgroup analyses. If any continuous covariate is found to be significant by the secondary outcome ANCOVA model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available. This table will use the same format as Table 18.1.1.

Table 39.1 Number of Underuse Days[a] ANCOVA Model Results: Full Analysis Set

Covariate	FAS Population (N=XXX) Number of Underuse Days (95% CI)	P-value
Age at Enrollment	xxx x (xxx x, xxx x)	x xx
Race		
White	xxx x (xxx x, xxx x)	x xx
Non-White	xxx x (xxx x, xxx x)	x xx
Sex		
Male	xxx x (xxx x, xxx x)	x xx
Female	xxx x (xxx x, xxx x)	x xx
Smoking Status		
Current	xxx x (xxx x, xxx x)	x xx
Former	xxx x (xxx x, xxx x)	x xx
Number of COPD Exacerbations	xxx x (xxx x, xxx x)	x xx

Covariate	Number of Underuse Days (95% CI)	FAS Population (N=XXX) P-value
COPD Exacerbation Severity		
Moderate	xxx x (xxx x, xxx x)	x xx
Severe/Very Severe	xxx x (xxx x, xxx x)	x xx
Prior Symbicort Treatment		
Symbicort Naïve	xxx x (xxx x, xxx x)	x xx
Symbicort Pre-treated	xxx x (xxx x, xxx x)	x xx
Time (months) on ICS/LABA Medication at Baseline		
Less than Six Months	xxx x (xxx x, xxx x)	x xx
Six or More Months	xxx x (xxx x, xxx x)	x xx
Group		
Control	xxx x (xxx x, xxx x)	x xx
Intervention	xxx x (xxx x, xxx x)	x xx
Device Time	xxx x (xxx x, xxx x)	x xx

[a]Underuse days is the number of study days a subject takes between one and three inhalations of their Symbicort medication on a given day. ANCOVA model based means are reported, Candidate covariates for the ANCOVA model were the significant covariates from the Adherent Symbicort Sensitivity analysis (Table 11.2.1). CI: Confidence Interval. COPD Severity Level: Moderate is FEV1 % predicted 50 – 79%, Severe/Very Severe is FEV1 % predicted < 50%.

Table 39.2 Number of Underuse Days[a] ANCOVA Analyses: Per-Protocol Analysis Set
Use same format as Table 39.1, but using PP. *Note: footnote will call out Table 11.2.2, instead*

Table 40.1 Number of Underuse Days[a] Subgroup Analyses: Full Analysis Set
For every covariate found to be significant in the ANCOVA model presented in Table 39.1 will then be included in the subgroup analyses. If any continuous covariate is found to be significant by the secondary outcome ANCOVA model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available. This table will use the same format as Table 18.1.1.

Table 40.2 Number of Underuse Days[a] Subgroup Analyses: Per-Protocol Analysis Set
For every covariate found to be significant in the ANCOVA model presented in Table 39.2 will then be included in the subgroup analyses. If any continuous covariate is found to be significant by the secondary outcome ANCOVA model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available. This table will use the same format as Table 18.1.1.

Table 41.1 Number of Overuse/Overuse Alert Days[a] ANCOVA Model Results: Full Analysis Set

Covariate	FAS Population (N=XXX) Number of OveruseOveruse Alert Days (95% CI)	P-value
Age at Enrollment	xxx x (xxx x, xxx x)	x xx
Race		
White	xxx x (xxx x, xxx x)	x xx
Non-White	xxx x (xxx x, xxx x)	x xx
Sex		
Male	xxx x (xxx x, xxx x)	x xx
Female	xxx x (xxx x, xxx x)	x xx
Smoking Status		
Current	xxx x (xxx x, xxx x)	x xx
Former	xxx x (xxx x, xxx x)	x xx
Number of COPD Exacerbations	xxx x (xxx x, xxx x)	x xx

Covariate	FAS Population (N=XXX) Number of Overuse Days (95% CI)	P-value
COPD Exacerbation Severity		
Moderate	xxx x (xxx x, xxx x)	x xx
Severe/Very Severe	xxx x (xxx x, xxx x)	x xx
Prior Symbicort Treatment		
Symbicort Naïve	xxx x (xxx x, xxx x)	x xx
Symbicort Pre-treated	xxx x (xxx x, xxx x)	x xx
Time (months) on ICS/LABA Medication at Baseline		
Less than Six Months	xxx x (xxx x, xxx x)	x xx
Six or More Months	xxx x (xxx x, xxx x)	x xx
Group		
Control	xxx x (xxx x, xxx x)	x xx
Intervention	xxx x (xxx x, xxx x)	x xx
Device Time	xxx x (xxx x, xxx x)	x xx

[a]Overuse/Overuse Alert days is the number of study days a subject takes between five or more inhalations of their Symbicort medication on a given day. ANCOVA model based means are reported, Candidate covariates for the ANCOVA model were the significant covariates from the Adherent Symbicort Sensitivity analysis (Table 11.2.1). CI: Confidence Interval. COPD Severity Level: Moderate is FEV1 % predicted 50 – 79%, Severe/Very Severe is FEV1 % predicted < 50%.

Table 41.2 Number of Overuse/Overuse Alert Days[a] ANCOVA Analyses: Per-Protocol Analysis Set
Use same format as Table 41.1, but using PP. *Note: footnote will call out Table 11.2.2, instead*

Table 42.1 Number of Overuse/Overuse Alert Days[a] Subgroup Analyses: Full Analysis Set
For every covariate found to be significant in the ANCOVA model presented in Table 41.1 will then be included in the subgroup analyses. If any continuous covariate is found to be significant by the secondary outcome ANCOVA model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available. This table will use the same format as Table 18.1.1.

Table 42.2 Number of Overuse/Overuse Alert Days[a] Subgroup Analyses: Per-Protocol Analysis Set
For every covariate found to be significant in the ANCOVA model presented in Table 41.2 will then be included in the subgroup analyses. If any continuous covariate is found to be significant by the secondary outcome ANCOVA model, dichotomization of the covariate for the subgroup analysis will be made after determining a clinically revelant cut point based on the data available. This table will use the same format as Table 18.1.1.

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Table 43. Concomitant Medications: Full Analysis Set

	Control Group (N=XXX)	Intervention Group (N=XXX)	Total (N=XXX)
Subjects with Concomitant Medication, n (%)	xxx (xx x)	xxx (xx x)	xxx (xx x)
AZDD 1, n (%)	xxx (xx x)	xxx (xx x)	xxx (xx x)
Preferred Term 1	xxx (xx x)	xxx (xx x)	xxx (xx x)
Preferred Term 2	xxx (xx x)	xxx (xx x)	xxx (xx x)
Preferred Term 3	xxx (xx x)	xxx (xx x)	xxx (xx x)
…etc.			
AZDD 2, n (%)	xxx (xx x)	xxx (xx x)	xxx (xx x)
Preferred Term 1	xxx (xx x)	xxx (xx x)	xxx (xx x)
Preferred Term 2	xxx (xx x)	xxx (xx x)	xxx (xx x)
Preferred Term 3	xxx (xx x)	xxx (xx x)	xxx (xx x)
…etc.			
AZDD 3, n (%)	xxx (xx x)	xxx (xx x)	xxx (xx x)
Preferred Term 1	xxx (xx x)	xxx (xx x)	xxx (xx x)
Preferred Term 2	xxx (xx x)	xxx (xx x)	xxx (xx x)
Preferred Term 3	xxx (xx x)	xxx (xx x)	xxx (xx x)
…etc.			
Etc.			

AZDD Version 16.2, AZDD: AstraZeneca Drug Dictionary. AZDD terms are sorted alphabetically and then preferred terms are sorted alphabetically within each AZDD term. A subject can have one or more AZDD term reported. A subject can have one or more preferred term reported under a given AZDD term, but will only counted once for each unique preferred term within a given AZDD term. Percentages are calculated using the number of non-missing observations (n) as the denominator. Concomitant medications are defined as medications that are taken by the subject on or after date of signed informed consent through post-study follow-up.

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Table 44.1 Symbicort Underuse, Overuse and Overuse Alert Days During the Study: Full Analysis Set

Puffs/Day	Number of Instances	Number of Subjects[a] n (%)	Percentage of Total Subject Days[b]	Percentage of Study Days > 4 Puffs/Day[c]	Cumulative Percentage of Study Days > 4 Puffs/Day
Less than 4 Puffs/Day (Underuse)	xxx	xxx (xx x%)	xx.x	NA	NA
4 Puffs/Day (Adherent)	xxx	xxx (xx x%)	xx.x	NA	NA
Greater than 4 Puffs/Day (Any Overuse)	xxx	xxx (xx x%)	xx.x	NA	NA
Greater than 10 Puffs/Day (Overuse Alert)	xxx	xxx (xx x%)	xx.x	NA	NA
Puffs/Day					
0	xxx	xxx (xx x%)	xx.x	NA	NA
1	xxx	xxx (xx x%)	xx.x	NA	NA
2	xxx	xxx (xx x%)	xx.x	NA	NA
:	:	:	:	:	:
5	xxx	xxx (xx x%)	xx.x	xx x	xx x
6	xxx	xxx (xx x%)	xx.x	xx x	xx x
7	xxx	xxx (xx x%)	xx.x	xx x	xx x
8	xxx	xxx (xx x%)	xx.x	xx x	xx x
9	xxx	xxx (xx x%)	xx.x	xx x	xx x
10	xxx	xxx (xx x%)	xx.x	xx x	xx x
:	:	:	:	:	:
16	xxx	xxx (xx x%)	xx.x	xx x	xx x
22	xxx	xxx (xx x%)	xx.x	xx x	100.0

[a] Percentage is based on the total number of subjects in the FAS.
[b]Percentage of Total Subject Days = (number of instances / total subject study days), for a given puff instance per day.
[c]Percentage of Study Days > 4 Puffs/Day = (number of instances / number of instances greater than 4 puffs/day), for a given puff instance per day.
NA: Not Applicable.

Table 44.2 Symbicort Underuse, Overuse and Overuse Alert Days During the Study: Per-Protocol Population
Use the same format as Table 44.1, but using PP

Table 45.1 Treatment Emergent Adverse Events by Group by Severity: Full Analysis Set

System Organ Class Preferred Term	Full Analysis Set (N=XXX)							
	Mild		Moderate		Severe		Total	
	Subjects n (%)	Events n (%)	Subjects n (%)	Events n (%)	Subjects n (%)	Events n (%)	Subjects n (%)	Events n (%)
INTERVENTION GROUP								
Number of Subjects with No AEs[a]	xxx (xx.x)		xxx (xx x)		xxx (xx x)		xxx (xx x)	
Number of Subjects with Any AE[a]	xxx (xx x)	xxx	xxx	xxx	xxx (xx x)	xxx	xxx (xx.x)	xxx
System Organ Class 1[b]	xxx (xx x)	xxx (xx x)	xxx (xx.x)	xxx (xx x)	xxx (xx x)	xxx (xx x)	xxx (xx.x)	xxx (xx.x)
Preferred Term 1[c]	xxx (xx x)	xxx (xx x)	xxx (xx.x)	xxx (xx x)	xxx (xx x)	xxx (xx x)	xxx (xx.x)	xxx (xx.x)
Preferred Term 2[c]	xxx (xx x)	xxx (xx x)	xxx (xx.x)	xxx (xx x)	xxx (xx x)	xxx (xx x)	xxx (xx.x)	xxx (xx.x)
Preferred Term 3[c]	xxx (xx x)	xxx (xx x)	xxx (xx.x)	xxx (xx x)	xxx (xx x)	xxx (xx x)	xxx (xx.x)	xxx (xx.x)
Etc…								
System Organ Class 2[b]	xxx (xx x)	xxx (xx x)	xxx (xx.x)	xxx (xx x)	xxx (xx x)	xxx (xx x)	xxx (xx.x)	xxx (xx.x)
Preferred Term 1[c]								
Preferred Term 2[c]	xxx (xx x)	xxx (xx x)	xxx (xx.x)	xxx (xx x)	xxx (xx x)	xxx (xx x)	xxx (xx.x)	xxx (xx.x)
Preferred Term 3[c]	xxx (xx x)	xxx (xx x)	xxx (xx.x)	xxx (xx x)	xxx (xx x)	xxx (xx x)	xxx (xx.x)	xxx (xx.x)
Etc…								
Etc…								
CONTROL GROUP								
:								

AE: Adverse Event; SOC: System Organ Class; MedDRA Version 20.0. A subject can have one or more SOC term reported. A subject can have one or more preferred term reported under a given SOC term.

[a]Percentages are calculated using the number of subjects in the full analysis set as the denominator.
[b]Percentages (subjects) are calculated using the number of subjects who reported at least one AE for a given severity as the denominator or (events) the number of events reported for a given severity as the denominator.
[c]Percentages (subjects) are calculated using the number of subjects who reported an AE in a given SOC as the denominator or (events) the number of events reported for a given severity in a given SOC as the denominator.

Programmer's note: [1] Repeat the entire table contents under 'INTERVENTION GROUP' for 'CONTROL GROUP' as well.[2]only include AEs that occurred after date of randomization in this table.

Table 45.2 Treatment Emergent Serious Adverse Events by Group by Severity: Full Analysis Set
Use the same format as Table 45.1, but using SAEs

Table 46.1 Treatment Emergent Adverse Events That Led to Study Discontinuation by Group by Severity: Full Analysis Set
Use the same format as Table 45.1, but subsets on only AEs that led to study discontinuation

Table 46.2 Treatment Emergent Serious Adverse Events That Led to Study Discontinuation by Group by Severity: Full Analysis Set
Use the same format as Table 45.1, but subsets on only SAEs that led to study discontinuation

Table 47.1 Pre-Treatment Emergent Adverse Events by Group by Severity: Full Analysis Set
Use the same format as Table 45.1, but includes only AEs that occurred before the Date of Randomization

Table 47.2 Pre-Treatment Emergent Serious Adverse Events by Group by Severity: Full Analysis Set
Use the same format as Table 45.1, but includes only SAEs that occurred before the Date of Randomization

Listing Shells

Each listing produced for the D589CL00003 study will have the following general layout. **Bolded text** will appear on each page of the figure. Details regarding the specific figure numbers, title and body content of the figure, and any footnote(s) are provided in the pages that follow.

Listing X Title of LISTING

Subject ID	Group	Variable[a]	Variable[b]	Variable[c]	Variable, Specify
Exxxxxxx	xxxxx	xxxxx	xxxxx	xxxxx	xxxxx

[a]Footnote. [b]Another footnote. [c]Yet another footnote.
Source Data: xxxx
Program: x:\xxx\xxx*programme*.sas (9.4) (ddmmmyyyy hh mm)

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Listing 1 Subject Disposition: Full Analysis Set

Subject ID	Group	Withdrawal/Completion Date	Was Subject Rescreened?	Did Subject Withdraw From the Study?	Did Subject Complete the Study?	Reason for Withdrawal
Exxxxxxx	Control	dd/mm/yyyy	Yes	Yes	No	Physician Decision

Listing 2.1 Protocol Deviations

Site	Subject ID	Group	Protocol Violation	Notes/Comments	Category of Protocol Violation	Screened Population	Full Analysis Set Population	Per-Protocol Analysis Set Population
xxxx	Exxxxxxx	Intervention	I/E criteria	Inclusion 03 & 04	Major	Yes	Yes	No
xxxx	Exxxxxxx	Control	I/E criteria	Exclusion 06	Major	Yes	Yes	No
xxxx	Exxxxxxx	Control	Symbicort supplied at randomization		Minor	Yes	Yes	Yes
xxxx	Exxxxxxx	Control	Technology issues	Unable to sync device	Minor	Yes	Yes	Yes

Programmer's note: Sort data by Protocol Violation and Subject ID

Listing 2.2 Analysis Populations

Subject ID	Group	Randomization Date	Initial Date Phone and Device Dispensed	Screened Population	Full Analysis Set Population	Per-Protocol Analysis Set Population
Exxxxxxx	Control	dd/mm/yyyy	dd/mm/yyyy	Yes	Yes	Yes
Exxxxxxx	Intervention	dd/mm/yyyy	dd/mm/yyyy	Yes	Yes	No

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Listing 3 Subject Demographics: Full Analysis Set

Subject ID	Group	Age at Enrollment (years)	Sex	Race	Ethnicity
Exxxxxxx	Intervention	xx	Male	Asian	Not Hispanic or Latino

Listing 4 Subject Vital Signs: Full Analysis Set

Subject ID	Group	Visit	Date of Assessment	Seated Pulse (beats/min)	Seated Blood Pressure (mmHg) Systolic/Diastolic	Respiratory Rate (breaths/min)	Temperature (°C)	Height (cm)	Weight (kg)
Exxxxxxx	Control	Baseline	dd/mm/yyyy	xxx	xxx/xxx	xxx	xxx x	xxx	xxx.x
		EOT	dd/mm/yyyy	xxx	xxx/xxx	xxx	xxx x	xxx	xxx.x

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Listing 5 Medical History: Full Analysis Set

Subject ID	Group	Visit	COPD Diagnosis Date	Most Recent Exacerbation Date	Number of COPD Exacerbations Within Past 12 Months	Most Recent FEV1	Most Recent FEV1/FVC	Hospitalized for Recent Exacerbation?	Hospitalized for >24 Hours for any Exacerbation Within Past 12 Months?	Medication Type	Treatment End Date
Exxxxxxx	Control	Baseline	dd/mm/yyyy	dd/mm/yyyy	xx	xxx	x.xx	No	Yes	Steroids	dd/mm/yyyy
		EOT	dd/mm/yyyy	dd/mm/yyyy	xx	xxx	x.xx	No	No	Steroids	dd/mm/yyyy

Subject ID	Group	Completed Physical Examination	Date of Physical Examination	Relevant Medical Condition	Relevant Surgery	Any Medical Condition/ Comorbidity?	System Organ Class	Condition (Preferred Term)
Exxxxxxx	Intervention	Yes	dd/mm/yyyy	Yes	No	Yes	xxxxx	xxxxx

Listing 6 Subject COPD History: Full Analysis Set

Subject ID	Group	Start Date/ End Date	Ongoing Condition	Currently Taking Medication for Condition?
Exxxxxxx	Intervention	dd/mm/yyyy	Yes	Yes

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Listing 7 Subject Smoking History: Full Analysis Set

Subject ID	Group	Smoker Status	Packs/Day	Years Cigarettes Consumed	Pack Years
Exxxxxxx	Intervention	Current	xx x	xx	xxx

Listing 8 BreatheMate Mobile App User Satisfaction Survey –Intervention Group: Full Analysis Set

Subject ID	Group	BreatheMate Mobile App Use	Easy to Use	Technical Difficulties	Receive Reminders	Clean Design	Reminders Were Helpful
Exxxxxxx	Intervention	Yes	Agree	Disagree	Strongly Disagree	Indifferent	Agree

Listing 9 SmartTouch Symbicort Device User Satisfaction Survey –Intervention Group: Full Analysis Set

Subject ID	Group	SmartTouch Symbicort Device Use	Easy to Use	Features Expected	Receive Reminders	Easy to Take On and Off	Great Look and Feel
Exxxxxxx	Intervention	Yes	Agree	Disagree	Strongly Disagree	Indifferent	Agree

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Listing 10 BreatheMate Web Portal User Satisfaction Survey – Investigator and Study Coordinator

ID	Role	BreatheMate Web Portal Use	Easy to Use	All Features Expect it to Have	Minimal Number of Clicks	Clean Design	Information is Easy to Find and Understand	Reminders Improve Subject Compliance	Improve Medication Refills	Helping Manage Condition
Exxxx999	Investigator	Yes	Agree	Disagree	Strongly Disagree	Indifferent	Agree	Disagree	Strongly Disagree	Indifferent
Exxxx999	Study Coordinator	Yes	Agree	Disagree	Strongly Disagree	Indifferent	Agree	Disagree	Strongly Disagree	Indifferent

Listing 11 CCQ: Full Analysis Set

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Subject ID	Group	Visit	Breathlessness at Rest	Breathlessness Physical Activities	Concerned About Breathing	Depressed About Breathing	Cough	Produce Phlegm	Strenuous Physical Activities	Moderate Physical Activities
Exxxxxxx	Intervention	Baseline	A few times	Several times	Many times	Never	Never	Never	Slightly limited	Very limited
		Week 1	A few times	Several times	Many times	Never	Never	Never	Slightly limited	Very limited

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Subject ID	Group	Visit	Daily Activities	Social Activities	Total Score	MCID Responder at EOT	Symptom Score	Functional State Score	Mental State Score
Exxxxxxx	Intervention	Baseline	Slightly limited	Extremely limited	x xx	Yes	x.xx	x.xx	x xx
		Week 1	Very limited	Not limited at all	x.xx*	-	x.xx	x.xx	x xx

MCID: Minimal Clinically Important Difference. *Indicates that the subject had a decrease in 0.4 units from his Baseline score and is considered a MCID responder for that week.

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Listing 12.1 Mean Number of Sets of Adherent Symbicort Puffs per Day

Subject ID	Group	Analysis Population(s)	Device Time on Study	Mean Number of Sets of Adherent Symbicort Puffs per Day for			
				Entire Study Period	Interval 1	Interval 2	Interval 3
Exxxxxxx	Intervention	FAS	xxx	x.xx	x xx	x.xx	x.xx
Exxxxxxx	Control	FAS/PP	xxx	x.xx	x xx	x.xx	x.xx

Interval 1: From study day 1 to study day 63 (inclusive); Interval 2: Study day 64 to study day 126 (inclusive); Interval 3: Study day 127 to EOT (inclusive).

Subject ID	Group	Analysis Population(s)	Total No Use Days	Proportion of No Use Days	Total Underuse Days	Proportion of Underuse Days	Total Adherent Days	Proportion of Adherent Days	Total Overuse Days	Proportion of Overuse Days	Total Overuse Alert Days	Proportion of Overuse Alert Days
Exxxxxxx	Intervention	FAS	xxx	x.xx	xxx	x.xx	xxx	x xx	xxx	x xx	xxx	x.xx
Exxxxxxx	Control	FAS/PP	xxx	x.xx	xxx	x.xx	xxx	x xx	xxx	x xx	xxx	x.xx

Interval 1: From study day 1 to study day 63 (inclusive); Interval 2: Study day 64 to study day 126 (inclusive); Interval 3: Study day 127 to EOT (inclusive).

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Listing 12.2 Mean Number of Symbicort Inhalations per Day

Subject ID	Group	Analysis Population(s)	Device Time on Study (Days)	Device Time on Study (Months)	Mean Number of Symbicort Inhalation per Day			
					Entire Study Period	Interval 1	Interval 2	Interval 3
Exxxxxxx	Intervention	FAS	xxx	xxx	x.xx	x xx	x xx	x xx
Exxxxxxx	Control	FAS/PP	xxx	xxx	x.xx	x xx	x xx	x xx

Listing 12.3 Mean Number of Complete Sets of Symbicort Puffs per Day

Subject ID	Group	Analysis Population(s)	Device Time on Study (Days)	Device Time on Study (Months)	Mean Number of Complete Stes of Symbicort Puffs per Day			
					Entire Study Period	Interval 1	Interval 2	Interval 3
Exxxxxxx	Intervention	FAS	xxx	xxx	x xx	x xx	x.xx	x xx
Exxxxxxx	Control	FAS/PP	xxx	xxx	x xx	x xx	x.xx	x xx

Listing 13 Symbicort Prescription Refills: Full Analysis Set

Subject ID	Group	Number of Symbicort Prescriptions Written	Total Symbicort Prescriptions Filled	Number of Symbicort Prescriptions Expected
Exxxxxxx	Intervention	xx	xx	xx
Exxxxxxx	Control	xx	xx	xx

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Listing 14 Concomitant Medications: Full Analysis Set

Subject ID	Group	Trade Name	AstraZeneca ATC	Preferred Term	Start Date	Stop Date or Ongoing	Total Daily Dose	Dose Unit	Dose Frequency	Route
Exxxxxxx	Intervention	xxxxx	xxxxx	xxxxx	dd/mm/yyyy	dd/mm/yyyy	xxxxxxx	g	Once	Nasal
		xxxxx	xxxxx	xxxxx	dd/mm/yyyy	Ongoing	xxxxxxx	%	QM	Oral
		xxxxx	xxxxx	xxxxx	dd/mm/yyyy	Ongoing	xxxxxxx	mg/kg	2 Times per Week	Topical
Exxxxxxx	Control	xxxxx	xxxxx	xxxxx	dd/mm/yyyy	dd/mm/yyyy	xxxxxxx	Tablet	Every Week	Oral
		xxxxx	xxxxx	xxxxx	dd/mm/yyyy	Ongoing	xxxxxxx	Puff	BID	Respiratory (Inhalation)

Listing 15 Adverse Events: Full Analysis Set

Subject ID	Group	Randomization Date	MedDRA SOC	MedDRA PT	Start Date/ End Date or Ongoing	AE Intensity	Outcome of AE	AE Caused by Symbicort	Symbicort Action	Concomitant Medication Taken?	AE Caused Withdrawal (Y/N)	SAE (Y/N)
Exxxxxxx	Control	dd/mm/yyyy	xxxxx	xxxxx	dd/mm/yyyy/ dd/mm/yyyy	Mild	Resolved	No	Dose Not Changed	Yes	No	No
			xxxxx	xxxxx	dd/mm/yyyy/ Ongoing	Moderate	Not Resolved	No	Dose Not Changed	Yes	No	No
Exxxxxxx	Intervention	dd/mm/yyyy	xxxxx	xxxxx	dd/mm/yyyy/ dd/mm/yyyy	Severe	Fatal	No	Drug Permanently Discontinued	No	No	Yes

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Listing 16 Serious Adverse Events: Full Analysis Set

Subject ID	Group	Randomization Date	MedDRA SOC	MedDRA PT	Start Date/ End Date or Ongoing	Date AE met Criteria for SAE	Date Investigator Became Aware of SAE	AE is Serious Due to	SAE Caused by Other Medication (Y/N) / if Yes Specify	SAE Caused by Study Procedure (Y/N) / if Yes Specify
Exxxxxxx	Intervention	dd/mm/yyyy	xxxxx	xxxxx	dd/mm/yyyy/ dd/mm/yyyy	dd/mm/yyyy	dd/mm/yyyy	Death	Yes/xxxxx	No
			xxxxx	xxxxx	dd/mm/yyyy/ Ongoing	dd/mm/yyyy	dd/mm/yyyy	Life Threatening	No	No
Exxxxxxx	Control	dd/mm/yyyy	xxxxx	xxxxx	dd/mm/yyyy/ dd/mm/yyyy	dd/mm/yyyy	dd/mm/yyyy	Requires hospitalization	No	No

Figure Shells

Each figure produced for the D589CL00003 study will have the following general layout. **Bolded text** will appear on each page of the figure. Details regarding the specific figure numbers, title and body content of the figure, and any footnote(s) are provided in the pages that follow.

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Figure X Title of Figure

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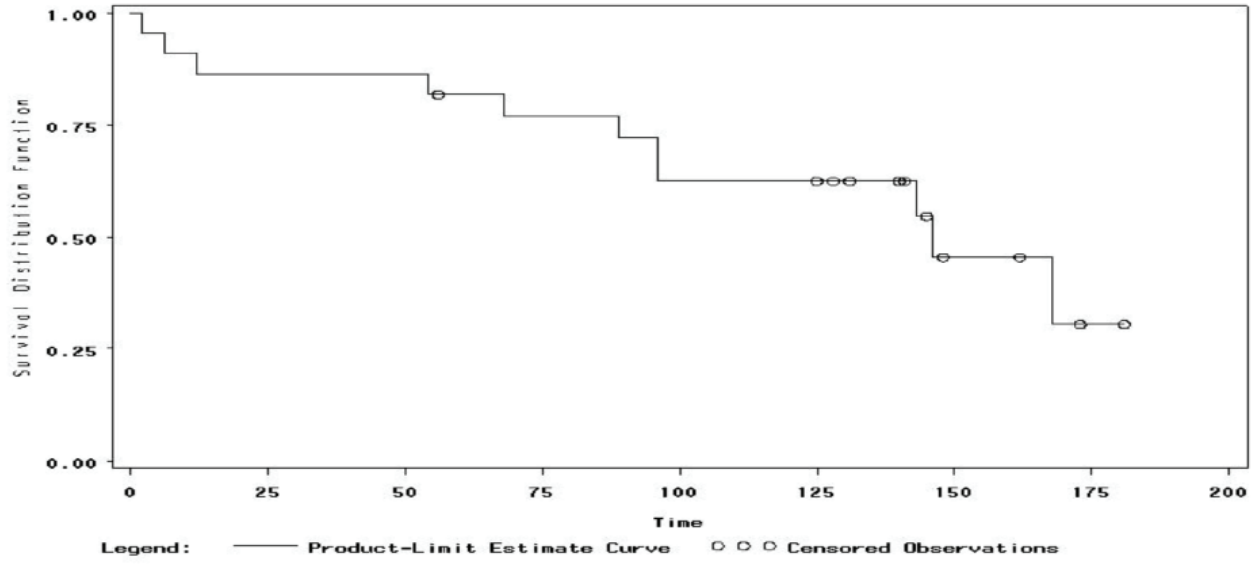
Figure 1 Kaplan-Meier Plot for Device Time on Study



Note that this figure is an example. The figure will have 4 lines for each treatment group and analysis population: Intervention (FAS), Control (FAS), Intervention (PP) and Control (PP). The y-axis title will be 'Proportion of Subjects Still in the Study', x-axis title will be 'Device Time on Study (months)' with the x-axis units of 0 to 6 in 1 month increments.