CLINICAL STUDY PROTOCOL

A Randomized, Single-Blind, Parallel-Group, Placebo-Controlled, Multidose Study Comparing the Therapeutic Equivalence of a 3M Inhaler and a Symbicort® Reference Inhaler, Each Delivering Budesonide/Formoterol Fumarate (80 µg/4.5 µg) in Adult Subjects With Asthma

Sponsor:	3M Health Care Ltd xxxxx United Kingdom
Sponsor Contact:	xxxxx xxxxx
Medical Monitor:	xxxxx xxxxx
24-Hour Safety Hotline (North America):	xxxxx
SAE Fax Number (North America):	xxxxx
Protocol Number:	CSP-07-000034
Study Phase:	Clinical Endpoint Bioequivalence Study
Version of Protocol:	Protocol Amendment 1, Version 2.0
Date of Protocol:	31 Oct 2016
Authors:	xxxxx
IND Number:	Not applicable

xxxxx

Declaration of Investigator

I have read and understood all sections of the protocol CSP-07-000034 entitled "A Randomized, Single-Blind, Parallel-Group, Placebo-Controlled, Multidose Study Comparing the Therapeutic Equivalence of a 3M Inhaler and a Symbicort® Reference Inhaler, Each Delivering Budesonide/Formoterol Fumarate (80 µg/4.5 µg) in Adult Subjects With Asthma."

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with Protocol Amendment 1, dated 31 Oct 2016, the International Council for Harmonisation guideline E6: Good Clinical Practice, and all applicable government regulations. I will not make changes to the protocol before consulting with 3M or implement protocol changes without institutional review board approval except to eliminate an immediate risk to subjects. I agree to administer study medication only to subjects under my personal supervision or the supervision of a subinvestigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Subject identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from 3M.

_____ _____

Signature of Investigator Date

_____

Printed Name of Investigator

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Protocol Synopsis

Protocol Number:	CSP-07-000034
Title:	A Randomized, Single-Blind, Parallel-Group, Placebo-Controlled, Multidose Study Comparing the Therapeutic Equivalence of a 3M Inhaler and a Symbicort® Reference Inhaler, Each Delivering Budesonide/Formoterol Fumarate (80 µg/4.5 µg) in Adult Subjects With Asthma
Sponsor:	3M Health Care Ltd (3M)
Study Phase:	Clinical Endpoint Bioequivalence Study
Study Centers Planned:	Approximately xxx study centers in the United States
Number of Subjects Planned:	Approximately 1470 adult subjects with asthma
Estimated Study Duration:	Each subject is expected to be in the study for approximately 8 to 10 weeks, which includes screening, a 2-week run-in period, and a 6-week treatment period. It is expected that the total duration of the study will be approximately 9 to 12 months.
Rationale:	The 3M Inhaler is being developed as a generic equivalent of the Symbicort® Reference Inhaler (80 µg /4.5 µg in order to provide a choice for patients, prescribers, and payers.
Objectives:	The primary objectives of this study are as follows: • To demonstrate the equivalence of the 3M Inhaler compared with a Symbicort Reference Inhaler in delivering budesonide/formoterol fumarate (80 µg/4.5 µg) • To demonstrate the superiority of the 3M Inhaler and the Symbicort Reference Inhaler compared with placebo • The safety object of this study is as follows: • To assess the safety of the 3M Inhaler compared with a Symbicort Reference Inhaler in delivering budesonide/formoterol fumarate (80 µg/4.5 µg) and compared with placebo

Efficacy Endpoints:	• Change from baseline in the area under the concentration-time curve of forced expiratory volume in 1 second (FEV_1) from zero up to 12 hours (AUC_{0-12}) at Day 1 • Change from baseline in FEV_1 measured in the morning at the end-of-treatment visit
Safety Endpoints:	• Number (percent), severity, and relatedness of adverse events (AEs) and serious adverse events
Subject Population:	Adult male or female subjects ≥18 years of age with a diagnosis of asthma, as defined by the National Asthma Education and Prevention Program, for at least 6 months. Subjects will have moderate-to-severe asthma with a pre-bronchodilator FEV_1 of ≥45% and ≤85% of predicted normal at least 6 hours after receiving a short-acting β2 agonist (SABA), as well as ≥15% reversibility of FEV_1 (14.5% to 14.99% will be rounded to 15%) and ≥0.20 L increase within 30 minutes following the administration of albuterol 360 µg. Chronic medications must be stable and subjects must be currently nonsmoking. Subjects must also be able and willing to perform peak expiratory flow assessments and enter diary information.
Study Design:	This is a randomized, single-blind, parallel-group, placebo-controlled, multidose study consisting of a 2-week run-in period followed by a 6-week treatment period using budesonide/formoterol delivered by the 3M Inhaler or the Symbicort Reference Inhaler and compared with placebo. Subjects will visit the study center at a screening, baseline, and end-of-treatment visits, and they will receive telephone contacts after 2 weeks and after 4 weeks of study treatment.
Efficacy Assessment:	Efficacy will be assessed via spirometry. Each subject will undergo spirometry assessments at the screening, baseline, and end-of-treatment/Week 6 visits.
Safety Assessment:	Safety will be assessed via AEs (seriousness, number [percent], severity, and relatedness).

Study Medication, Dosage, and Route of Administration:	During the run-in period, study medication will consist of a run-in (placebo) inhaler. During the treatment period, study medication will include randomized treatment with either a metered-dose inhaler containing a combination of budesonide (80 µg) and formoterol (4.5 µg) using the 3M Inhaler or the Symbicort Reference Inhaler, or a metered-dose inhaler containing placebo. Regardless of treatment, study medication will be administered as 2 inhalations each given twice daily (morning and evening, approximately 12 hours apart).
Statistical Methods:	Statistical analysis will be performed using SAS® software Version 9.2 or later. Summary statistics of the data collected will be provided by treatment (3M Inhaler, Symbicort Reference Inhaler, and placebo). Continuous variables will be summarized using the mean, SD, coefficient of variance, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. Data will be listed in data listings. Details of the statistical analyses, methods, and data conventions will be further described in the statistical analysis plan.
Date of Protocol:	31 Oct 2016

List of Abbreviations

Abbreviation	Definition
3M	3M Health Care Ltd
AE	adverse event
AUC_{0-12}	area under the concentration-time curve from zero up to 12 hours
CFR	Code of Federal Regulations
CV	coefficient of variance
CYP	cytochrome P450
eCRF	electronic case report form
FAS	full analysis set
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
HFA	hydrofluoroalkane
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	institutional review board
xxx	
LABA	long-acting β agonist
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
NAEPP	National Asthma Education and Prevention Program
xxx	
xxx	
pMDI	pressurized metered-dose inhaler
PPS	per-protocol set
SABA	short-acting β2 agonist
SAE	serious adverse event
SAP	statistical analysis plan

1 Introduction

Asthma is a common respiratory disease. It is characterized by chronic airway inflammation leading to airflow obstruction with symptoms such as breathlessness, cough, impairment of physical activity, and potentially death. Prevalence data in the United States between 2001 and 2010 indicated an overall increase in asthma during the period [Akinbami, 2012], and by 2014, there were 24 million people with asthma [CDC, 2016].

Inhaled corticosteroids have been widely used as a safe and effective anti-inflammatory therapy for the treatment of persistent asthma for many years. Inhaled corticosteroids are recommended as the maintenance treatment of choice in treatment guidelines (ie, Global Initiative for Asthma [GINA] and the National Heart, Lung, and Blood Institute National Asthma Education and Prevention Program [NAEPP]) in all but patients with mild intermittent asthma whose symptoms are adequately maintained on short-acting β2 agonists (SABAs) alone [GINA, 2016; NAEPP, 2007].

Long-acting β agonists (LABAs) have also been widely used as safe and effective bronchodilator therapy for the treatment of persistent asthma for many years, and they are also recommended as a maintenance therapy in conjunction with inhaled corticosteroids [GINA, 2016; NAEPP, 2007] for patients with moderate to severe asthma who remain symptomatic despite low-dose inhaled corticosteroids and SABAs (as needed).

Symbicort® is approved by the US Food and Drug Administration (FDA) as a combination product containing a corticosteroid and a LABA and is indicated for the treatment of asthma patients 12 years of age and older and for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease including chronic bronchitis and emphysema. It is not indicated for the relief of acute bronchospasm. It is available as a pressurized metered-dose inhaler (pMDI) containing a combination of budesonide (80 or 160 µg) and formoterol (4.5 µg) as an inhalation aerosol and is administered as 2 inhalations twice daily (morning and evening, approximately 12 hours apart) [Symbicort, 2016].

3M Health Care Ltd (3M) is developing a drug product (3M Inhaler) that is a pMDI containing a combination of budesonide (80 µg) and formoterol (4.5 µg) as an inhalation aerosol. The 3M Inhaler is expected to be equivalent to the currently available Symbicort (referred to in this protocol as Symbicort Reference Inhaler) in terms of reproducibility of delivery of both emitted and respirable dose of medication. The 3M Inhaler is being

developed as a generic equivalent of the Symbicort Reference Inhaler in order to provide a choice for patients, prescribers, and payers.

This study was designed in accordance with the FDA guidance on budesonide/formoterol fumarate dihydrate [FDA, 2015], and this clinical endpoint study is intended to establish bioequivalence between the 3M Inhaler and the Symbicort Reference Inhaler.

2 Study Objectives and Endpoints

Objectives	Endpoints
The primary objectives of this study are as follows: • To demonstrate the equivalence of the 3M Inhaler compared with a Symbicort Reference Inhaler in delivering budesonide/formoterol fumarate (80 µg/4.5 µg) • To demonstrate the superiority of the 3M Inhaler and the Symbicort Reference Inhaler compared with placebo	• Change from baseline in the area under the concentration-time curve of forced expiratory volume in 1 second (FEV_1) from zero up to 12 hours (AUC_{0-12}) at Day 1 • Change from baseline in FEV_1 measured in the morning at the end-of-treatment visit
The safety object of this study is as follows: • To assess the safety of the 3M Inhaler compared with a Symbicort Reference Inhaler in delivering budesonide/formoterol fumarate (80 µg/4.5 µg) and compared with placebo	• Number (percent), severity, and relatedness of adverse events (AEs) and serious adverse events (SAEs)

3 Investigational Plan

3.1 Schedule of Events

Procedure	Screening Visit[1]	Baseline Visit	Telephone Contacts		End of Treatment
Visit Day/Window	-21 days to -14 days	Day 1 (12-hour visit)	Day 14 ±2 days	Day 28[2] ±2 days	Day 42 ±2 days
Informed consent	X				
Medical history	X				
Demographics	X				
Electrocardiogram	X				
Safety laboratory assessment (obtained locally)	X				X
Physical examination (with height [screening only] and weight)	X				X
Pregnancy test[3]	X	X			X
Vital sign (blood pressure and heart rate) assessments	X	X			X
Spirometry assessments[4]	X	X			X
Inclusion/exclusion criteria review	X	X			
Randomization xxx		X			
Inhaler training	X	X			
Dispense run-in period inhaler	X				
Dispense rescue therapy inhaler[5]	X	X			
Dispense study medication		X			
Concomitant medications	X	X	X	X	X
Adverse event monitoring	X	X	X	X	X
Training xxx	X				
Study medication compliance and diary monitoring (retraining, as needed)		X	X	X	
Diary collection					X

[1] Following the screening visit, there will be 14- to 21-day run-in period. If needed, subjects can also rescreen. See Section 3.2 for additional details on the run-in period and on rescreening.

[2] At the Day 28 (Week 4) visit, subjects will be instructed to switch to the second inhaler beginning with the evening dose on the day of the telephone visit. Subjects will be reminded not to take study medication within 12 hours (±2 hours) of the start time of their end-of-treatment visit.

[3] For females of childbearing potential only, a urine pregnancy test must be conducted at the screening and baseline visits, and a serum pregnancy test must be obtained at the screening and end-of-treatment visits. See Appendix 2 for a definition of childbearing potential.

[4] See Section 6.1 for details on each spirometry assessment.

[5] Ensure that the subject has enough rescue therapy (see Section 5.2.2) for the remainder of the study.

3.2 Study Design

This is a randomized, single-blind, parallel-group, placebo-controlled, multidose study consisting of a 2-week run-in period followed by a 6-week treatment period using budesonide/formoterol delivered by the 3M Inhaler or the Symbicort Reference Inhaler and compared with placebo. Subjects will visit the study center at a screening, baseline, and end-of-treatment visits, and they will receive telephone contacts after 2 weeks and after 4 weeks of study treatment.

3.2.1 Screening Visit

Subjects will undergo the procedures outlined in the Schedule of Events (Section 3.1).

Two spirometry assessments will occur at the screening visit and must be conducted between 0400 and 1100 (ie, 4:00 AM and 11:00 AM) (see Section 6.1). Subjects cannot have taken a LABA within 24 hours of the spirometry assessment and they cannot have taken rescue medication within 6 hours of the spirometry assessment; if these requirements are not met, the visit must be rescheduled. If a subject does not meet the spirometry assessment criteria outlined in the inclusion criteria (see Section 4.1.1), a repeat spirometry assessment may occur within 7 days. The repeat assessment must be conducted at the same time of day (±1 hour) as the original spirometry screening assessment. Subjects who meet the spirometry requirements upon repeat testing can enter the run-in period (provided they meet all other inclusion criteria and none of the exclusion criteria). Additional screening assessments outlined in the Schedule of Events do not need to be repeated if they were performed within the past 7 days.

Subjects who consent to participate and who meet the entry criteria will enter the run-in period. This run-in period will be used to washout prestudy medications and to establish an FEV_1 baseline value. See Appendix 1 for a complete list of washout medications and the required washout period for each. Some medications (such as immunosuppressive therapy) require more than 14 days of washout. If more than 21 days of washout are needed, subjects will be considered a screen failure. However, subjects who have failed screening due to the need for an extended medication washout may be subsequently rescreened 1 additional time.

During the screening visit, subjects will be given instructions on how to use the run-in period inhaler, and subjects will be informed that compliance to the run-in period inhaler schedule

will be checked at the baseline visit. Subjects will also be observed and trained until they are able to use the run-in medication properly. Subjects will take home a run-in period inhaler for use during the run-in period.

Subjects will be given a SABA inhaler (see Section 5.2.2) to be used throughout the study as rescue therapy for the treatment of acute episodes of bronchospasm or shortness of breath. In addition, xxx collect diary information twice daily (at home), in the morning and in the evening, approximately 12 hours apart, throughout the study (see Section 6.2.1). Subjects will be observed to ensure that they are able to use the device properly.

3.2.2 Run-In Period

The run-in period will be 14 to 21 days in duration, depending on the washout needs of each subject. During the run-in period, subjects will receive a run-in period (placebo) inhaler from which they will administer 2 inhalations twice daily (morning and evening, approximately 12 hours apart). They will xxx collect diary information twice daily throughout the run-in period.

3.2.3 Baseline Visit

Following the run-in period, subjects will come to the clinic for a baseline visit that will include 12 hours of serial spirometry assessments; the first predose baseline assessment (ie, 30 minutes before dosing) must begin between 0400 and 1100 (ie, 4:00 AM and 11:00 AM). Note: When setting the start time for the baseline visit, consider that not only does the baseline visit include 12 hours of serial spirometry testing but also that the spirometry assessment during the end-of-treatment visit must occur within 1 hour from the first predose baseline spirometry assessment (ie, 30 minutes before initial dosing).

Subjects will be instructed to **not** use the run-in period inhaler on the day of the baseline visit and, if possible, to not take rescue medication within 6 hours of the start of the baseline visit; if a subject is unable to withhold rescue medication, the visit must be rescheduled.

Prior to randomization, study center personnel will calculate compliance with the run-in period inhaler schedule using xxx number of run-in period inhalations used as well as the number of rescue therapy inhalations xxx Study medication, diary, and

compliance re-education should be provided as needed. xxxxx

Prior to randomization, the study center personnel must review the inclusion and exclusion criteria, as appropriate, to confirm that each subject qualifies to continue in the study. This includes performing 2 pulmonary function tests 30 minutes apart to assess FEV_1 (see Section 6.1).

Qualified subjects will be randomized xxx in a 3:3:1 ratio to receive the 3M Inhaler, the Symbicort Reference Inhaler, or placebo, respectively. Following randomization, subjects will undergo the procedures outlined in the Schedule of Events (Section 3.1).

Subjects will be given instructions on how to use the treatment period inhalers, xxx. Subjects will also be observed to ensure that they are able to use the study medication properly, and re-education will be provided as necessary.

3.2.4 Telephone Contacts (Week 2 and Week 4)

There will be 2 separate telephone contacts during this study to assess safety and determine if the subject has had any new AEs, changes to ongoing AEs (including discontinuation or exacerbation of an AE), or changes to their concomitant medications, whether or not the changes were recorded in the diary. If a subject indicates that changes occurred but were not recorded in the diary, the study center personnel will re-educate the subject on capturing information in the diary.

The first telephone contact will occur at Week 2 (Day 14 ± 2 days), and the second telephone contact will occur at Week 4 (Day 28 ± 2 days). At the baseline visit, subjects will be given 2 canisters of study medication, clearly labeled as Canister 1 and Canister 2, based on their randomized treatment (3M Inhaler, Symbicort Reference Inhaler, or placebo). Subjects will use Canister 1 until the Week 4 telephone call visit. At the Week 4 telephone visit, subjects will be instructed to switch to Canister 2 beginning with the evening dose on the day of the telephone visit and use that canister for the remainder of the study. (If a subject needs to switch to Canister 2 for any reason prior to the Week 4 telephone contact, the subject must notify study center personnel so that study medication compliance can be calculated correctly.)

Subjects will also be reminded that no study medication should be taken within 12 hours (±2 hours) of the start time of their end-of-treatment visit.

3.2.5 End-of-Treatment Visit (Week 6)

Following 6 weeks of treatment, subjects will come into the clinic for an end-of-treatment visit (Day 42 ± 2 days). At the end-of-treatment visit, subjects will have 2 spirometry assessments. The first spirometry assessment will be conducted at the same time of day (±1 hour) as the first predose baseline spirometry assessment (ie, 30 minutes before initial dosing); the second spirometry assessment will be performed 30 minutes (±5 minutes) later.

Subjects will be instructed **not** to take study medication within 12 hours of the start of their end-of-treatment visit and not to take rescue medication within 6 hours of the start of the visit. If a subject is unable to withhold rescue medication or inadvertently took study medication within 12 hours of the start of their end-of-treatment visit, the visit must be rescheduled. Subjects will undergo the procedures outlined in the Schedule of Events (Section 3.1).

Subjects must bring both canisters of study medication so that study center personnel can confirm study medication compliance. Study center personnel will also review the diary information and speak with the subject to determine if the subject has had any new AEs, changes to ongoing AEs (including discontinuation or exacerbation of an AE), or changes to their concomitant medications, whether or not the changes were recorded in the diary.

Subjects who discontinue the study early will attend the end-of-treatment visit upon termination. Any ongoing SAE or AE that led to study discontinuation will continue to be followed up after the end-of-treatment visit until satisfactory resolution, the investigator deems the event to be chronic or not clinically significant, or the subject is considered to be stable.

This study will be considered complete when the last subject has completed the last end-of-treatment visit or additional AE follow-up as necessary.

4 Subject Selection and Withdrawal Criteria

4.1 Selection of Study Population

Approximately 1470 adult subjects with asthma will be enrolled at approximately xxx study centers in the United States. Subjects will be assigned to study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria. Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Each subject is expected to be in the study for approximately 8 to 10 weeks, which includes screening, a 2-week run-in period, and a 6-week treatment period. It is expected that the total duration of the study will be approximately 9 to 12 months.

4.1.1 Inclusion Criteria

Each subject must meet all of the following criteria to be enrolled in this study:

1. Is capable of understanding the written informed consent, provides signed and witnessed written informed consent, and agrees to comply with protocol requirements

2. Is a male or female □18 years of age

3. If female, is of non-childbearing potential or of childbearing potential and committed to consistent and correct use of an acceptable method of birth control (see Appendix 2 for additional information on contraception)

4. Has been diagnosed by a physician to have asthma, as defined by the NAEPP [NAEPP, 2007] at least 6 months prior to screening for study participation

5. Has moderate-to-severe asthma with a prebronchodilator FEV_1 of ≥45% and ≤85% of predicted normal, measured at least 6 hours after receiving a SABA and at least 24 hours after the last dose of a LABA, at the screening and baseline visits

6. Has ≥15% reversibility of FEV_1 (14.5% to 14.99% will be rounded to 15%) and ≥0.20 L increase within 30 minutes following the administration of albuterol 360 µg delivered via a pMDI with a spacer (see Section 6.1)

7. Has stable asthma control on a chronic asthma treatment regimen (mono- or combination therapy) for at least 4 weeks prior to the screening visit

8. Is currently nonsmoking; has not used tobacco products (ie, cigarettes, cigars, pipe tobacco, E-cigarettes, other inhaled nicotine) within the past year, and has less than 10 pack-years of historical use

9. Is able to replace current regularly scheduled SABA with albuterol hydrofluoroalkane (HFA) pMDI 90 µg for use only on an as-needed basis for the duration of the study (subjects should be able to withhold all inhaled SABAs for at least 6 hours prior to lung function assessments on study visit days)

10. Is willing to discontinue current asthma medications (inhaled corticosteroids and LABAs), as well as the prohibited medications listed in Appendix 1, during the run-in period and for the remainder of the study

11. Is able and willing to xxx enter diary information twice daily (at home) with a handheld device.

4.1.2 Exclusion Criteria

A subject meeting any of the following criteria will be excluded from the study:

1. If female, is pregnant or lactating/breastfeeding, as well as those not postmenopausal (no menses for the previous 24 months), surgically sterile, or practicing an effective method of birth control (see Appendix 2 for additional information on contraception)

2. Has life-threatening asthma, defined as a history of asthma episode(s) requiring intubation, and/or associated with hypercapnoea, respiratory arrest or hypoxic seizures, asthma-related syncopal episode(s), emergency room/urgent care clinic visit, or hospitalizations within the past year or during the run-in period

3. Has significant respiratory disease other than asthma (eg, chronic obstructive pulmonary disease, interstitial lung disease, etc.)

4. Has evidence or history of a clinically significant cardiovascular disease or abnormality, including congestive heart failure, uncontrolled hypertension, uncontrolled coronary artery disease, myocardial infarction, or cardiac dysrhythmia

5. Has historical or current evidence of clinically significant hematologic, hepatic, neurologic, psychiatric, renal, or other diseases that, in the opinion of the investigator,

would put the subject at risk through study participation, or would affect the study analyses if the disease exacerbated during the study

6. Has required systemic corticosteroids (for any reason) within the past 4 weeks or during the run-in period

7. Is hypersensitive to any sympathomimetic drug (eg, formoterol or albuterol); any inhaled, intranasal, or systemic corticosteroid therapy; or any excipients in the study medication (including HFA, povidone, and polyethylene glycol)

8. Is currently receiving β blockers

9. Has a current diagnosis or history of hepatitis B, hepatitis C, or human immunodeficiency virus as determine by laboratory testing at Screening, or active tuberculosis as determined by medical history and physical examination

10. Is currently smoking, has had tobacco products within the last year, or has a tobacco smoking history of 10 pack-years or more

11. Currently smokes marijuana or has used marijuana within the previous 30 days prior to screening

12. Has evidence of a viral or bacterial upper or lower respiratory tract infection, or sinus or middle ear infection within 4 weeks of screening

13. Has untreated oropharyngeal candidiasis at the screening visit

14. Has a history of alcohol or drug abuse within the year prior to screening

15. Has had treatment with any other investigational drug within 5 half-lives (if known), otherwise a minimum of 30 days prior to screening, or has any plans to participate in another investigational drug study at any time during this study

16. Has been treated with any known strong cytochrome P450 (CYP) 3A4 inhibitors (eg, ketoconazole, ritonavir, clarithromycin) within 30 days before the screening visit, or plans to be treated with any strong CYP3A4 inhibitor during study participation

17. Is an employee or family member of the investigator or study center personnel

18. Has any condition or other factor that in the investigator's opinion may limit compliance to study procedures, dosing intervals, or study visits

19. Has previously been randomized in 3M study CSP-07-000034

4.2 Withdrawal of Subjects From the Study

The duration of the study is defined for each subject as the date signed written informed consent is provided through the end-of-treatment visit (or the last follow-up visit if the subject is withdrawn due to an AE; see Section 6.2.3.6). If a subject is withdrawn from the study due to an AE, the event will be followed up after the end-of-treatment visit until satisfactory resolution, the investigator deems the event to be chronic or not clinically significant, or the subject is considered to be stable; this follow-up is also required for SAEs.

4.2.1 Reasons for Withdrawal/Discontinuation

Subjects may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study center. Every effort should be made to keep subjects in the study. The reasons for subjects not completing the study will be recorded. A subject may be withdrawn from the study for any of the following reasons:

1. The subject does not meet the protocol inclusion or exclusion criteria
2. The subject demonstrates noncompliance to the protocol, including during the run-in period
3. A serious or intolerable AE that in the investigator's opinion requires withdrawal from the study. (Upon the occurrence of a serious or intolerable AE, the investigator must confer with the medical monitor)
4. Symptoms or an intercurrent illness not consistent with the protocol requirements or that justifies withdrawal, including significant respiratory tract infection or exacerbation of asthma symptoms severe enough to warrant additional medications
5. The subject is lost to follow-up
6. Other (eg, pregnancy, development of contraindications of use of study medication)

7. The subject withdraws consent or the investigator or sponsor decides to discontinue the subject's participation in the study

8. 3M terminates the study

4.2.2 Handling of Withdrawals

Subjects are free to withdraw from the study at any time upon request. Subject participation in the study may be stopped at any time at the discretion of the investigator or at the request of the sponsor. If study medication is permanently stopped by the subject or investigator (ie, no additional study medication will be taken by the subject), the subject will be removed from the study.

When a subject withdraws from the study, the reason(s) for withdrawal must be recorded in the electronic case report form (eCRF). Whenever possible, all subjects who withdraw from the study prematurely will undergo all end-of-treatment assessments (see Section 3.1). Subjects who fail to return for final assessments will be contacted by the study center in an attempt to have them comply with the protocol.

If a subject does not return for a scheduled visit, every effort will be made to contact the subject. This follow-up will include 2 documented telephone calls from the study center personnel to the subject, followed by 1 registered letter requesting that the subject contact the study center to complete all follow-up procedures.

The investigator will inquire about the reason for withdrawal, request that the subject return all study medication, request that the subject return for a final visit, and subsequently follow up with the subject on any unresolved AE. It is vital to obtain follow-up data on any subject withdrawn because of an AE.

5 Study Treatments

5.1 Method of Assigning Subjects to Treatment Groups

Subjects will be randomly assigned to receive budesonide/formoterol fumarate (80 µg/4.5 µg) via a 3M Inhaler, budesonide/formoterol fumarate (80 µg/4.5 µg) via a Symbicort Reference Inhaler, or placebo using a 3:3:1 allocation ratio. xxx.

5.2 Treatments Administered

The 3M Inhaler, the Symbicort Reference Inhaler, and placebo inhalers (for both the run-in and treatment periods) will be supplied by 3M or its designee. The run-in period inhalers will be shipped in a separate box clearly labeled for use during the run-in period. Study center personnel must not dispense placebo inhalers from the treatment box in place of the run-in period inhalers and must not dispense the run-in period inhalers during the treatment period.

The following treatments will be administered during the study:

- Placebo via a placebo inhaler (over the 2-week run-in period, 2 inhalations twice daily)
- Budesonide/formoterol fumarate (80 µg/4.5 µg) via the 3M Inhaler (over the 6-week treatment period, 2 inhalations twice daily)
- Budesonide/formoterol fumarate (80 µg/4.5 µg) via the Symbicort Reference Inhaler (over the 6-week treatment period, 2 inhalations twice daily)
- Placebo via a placebo inhaler (over the 6-week treatment period, 2 inhalations twice daily)

Subjects will be instructed to rinse their mouths with water without swallowing after study medication administration in the morning and in the evening.

Of note, the 3M Inhaler and the Symbicort Reference Inhaler include formoterol, a LABA, as an active ingredient. Clinical studies have shown that LABA medicines such as formoterol increase the risk of death from asthma complications. It is not known whether budesonide, the other active ingredient in the 3M Inhaler and the Symbicort Reference Inhaler, reduces the risk of death from asthma complications seen with formoterol.

5.2.1 Administration of Study Medication

Symbicort is an FDA-approved medication, and administration information can be found in the package insert [Symbicort, 2016].

At the screening visit, subjects will be provided with detailed instructions on how to administer the study medication. They will demonstrate to study center personnel their ability to correctly use the product. During the 2-week run-in period, subjects will use a run-in (placebo) inhaler. The first run-in dose will be administered at the study center at the end of the screening visit.

For the day of the baseline visit, subjects will be instructed not to take their morning dose from the run-in (placebo) inhaler prior to attending the visit. At the baseline visit, eligible subjects will receive 2 canisters of study medication, clearly labeled as Canister 1 and Canister 2, with randomized treatment after the first (predose) spirometry assessment. Subjects will take their morning dose on the first day of treatment in the presence of study center personnel. The evening dose of study medication on the day of the baseline visit will be taken 12 hours after the morning dose.

All subsequent doses of study medication will be taken in the morning and evening during the 6-week study period. Subjects will be instructed to take their medication around the same time each day with approximately 12 hours between doses. If a subject misses a dose, the dose may be taken late if it is within 6 hours of the target time of the missed dose and at least 6 hours from the target time of the next dose (ie, doses cannot be taken less than 6 hours apart).

Subjects will take study medication as directed from Canister 1 until the telephone contact visit at Week 4, at which point they will be instructed to switch to Canister 2, beginning with the evening dose on the day of the telephone visit, and they will use Canister 2 for the remainder of the study. (If a subject needs to switch to Canister 2 for any reason prior to the

Week 4 telephone contact, the subject must notify study center personnel so that study medication compliance can be calculated correctly.)

The last dose of study medication will be the day before the end-of-treatment visit. When subjects are contacted for the Week 4 telephone visit, they will be reminded that no study medication should be taken within 12 hours (±2 hours) of the start time of their end-of-treatment visit and to bring back both canisters to the study center for their visit.

5.2.2 Rescue Therapy

A SABA inhaler (albuterol HFA pMDI 90 µg) will be provided to subjects by the study center for use as rescue medication during the study.

Subjects will record the number of inhalations (puffs used) of rescue medication (albuterol HFA pMDI 90 µg) each morning and evening in the diary. The average number of daily inhalations over the 7 days before the baseline visit will be the baseline value and will be compared with the rescue medication use during the 6-week treatment period. Rescue-free days are defined as 24-hour periods with no rescue medication usage.

Subjects who experience an asthma exacerbation, including excessive SABA use (see Section 6.2.2) should be reassessed by the investigator for potential worsening asthma and to determine if the subject should be withdrawn from the study.

If a subject requires rescue medication during the postdose serial spirometry assessment period of the baseline visit, the event will be recorded as an AE and the medication used will be recorded as a concomitant medication in the eCRF; the date and time of administration as well as the number of puffs will be recorded. These subjects may continue in the study.

5.2.3 Inhaler Functionality

If a subject suspects that an inhaler is not working properly, the subject should immediately contact study center personnel. All inhalers suspected of not working properly will be sent back to 3M for further evaluation.

5.3 Identity of Investigational Product

The 3M Inhaler is a pMDI containing a combination of budesonide (80 µg) and formoterol (4.5 µg) as an inhalation aerosol. The 3M Inhaler also contains the following inactive excipients: xxx. Each inhaler contains 120 actuations per canister.

The Symbicort Reference Inhaler is a pMDI containing a combination of budesonide (80 µg) and formoterol (4.5 µg) as an inhalation aerosol. The Symbicort Reference Inhaler contains the following inactive excipients: xxx. Each inhaler contains 120 actuations per canister.

The placebo inhaler is identical in appearance to the 3M Inhaler. It is a pMDI containing placebo as an inhalation aerosol. The placebo inhaler contains xxx. Each inhaler contains 120 actuations per canister.

The sponsor (3M) or its designee will provide adequate supplies of study medication to the study centers.

5.4 Management of Clinical Supplies

5.4.1 Study Medication Packaging and Storage

Budesonide/formoterol (80 µg/4.5 µg) to be used with the 3M Inhaler and the Symbicort Reference Inhaler, along with placebo, will be prepared and shipped by 3M or its designee.

Each budesonide/formoterol kit xxx

All study medication must be stored in a secure area, protected from moisture, and kept at a controlled room temperature between 68°F and 77°F (20°C and 25°C).

5.4.1.1 Priming the Inhalers

Each inhaler should be primed before the first use xxx. To prime an inhaler, 2 test sprays should be released into the air away from the face, with the inhaler shaken well for 5 seconds before each spray.

5.4.2 Study Medication Accountability

The investigator will maintain accurate records of receipt of all study medication, including dates of receipt. In addition, accurate records will be kept regarding when and how much study medication is dispensed and used by each subject in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding study medication accountability, all study medication will be reconciled and retained or destroyed according to applicable regulations.

5.4.3 Retention Samples

Per the FDA Guidance for Industry [DHHS, 2004], study centers must maintain retention samples that may be accessed by the FDA.

xxxxx

5.5 Overdose Management

An overdose is any dose of study medication given to a subject or taken by a subject that exceeds the dose described in the protocol. Any overdose, with or without associated AEs, must be promptly reported to the medical monitor. Overdoses without signs or symptoms do not need to be recorded as AEs; in case of any AEs associated with the overdose, these will be reported on the relevant AE or SAE sections, as applicable, in the eCRF.

5.6 Blinding

This is a single-blind study. xxxxx

5.7 Treatment Compliance

Subject compliance will be assessed at the baseline visit (for the run-in period inhaler) and at the end-of-treatment visit (for the study medication inhaler) using the dose counter on each

inhaler. The diaries will also be used as a source for subject compliance, particularly when the study medications are not returned. xxxxx

6 Study Assessments and Procedures

Before performing any study procedures, all potential subjects will sign an informed consent form (ICF). Subjects will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the subject. The investigator and a witness will also sign the ICF.

As shown in the Schedule of Events (Section 3.1), subjects will have evaluations at screening, baseline, Week 2, Week 4, and end-of-treatment (Week 6) visits. The Week 2 and Week 4 evaluations are telephone contacts from the study center personnel, during which subjects will be queried regarding changes to their concomitant medications and AE experiences (new AEs or changes to ongoing AEs [including discontinuation or exacerbation of AEs]), whether or not the changes were recorded in the diary. If a subject indicates that changes occurred but were not recorded in the diary, the study center personnel will re-educate the subject on capturing information in the diary.

At the Week 4 telephone contact, subjects will also be reminded to switch to Canister 2 and to not take study medication within 12 hours of their end-of-treatment visit.

6.1 Efficacy Assessments

The primary efficacy endpoints are described in Section 7.1.1.

Lung function will be assessed using spirometry xxx. Each subject will undergo lung function assessments at the screening, baseline, and end-of-treatment visits. At the screening visit, subjects cannot have taken a LABA within 24 hours of the first spirometry assessment; at the end-of-treatment visit, subjects cannot have taken study medication within 12 hours before the first spirometry assessment. In addition, for all visits where lung function is tested, subjects cannot have taken rescue medication within 6 hours of the first spirometry assessment of each visit; if these requirements are not met, the spirometry assessments must be rescheduled.

At the screening visit, subjects will have 2 spirometry assessments. The screening assessments will be completed in the morning. The first spirometry assessment will be conducted to assess the subject's FEV_1 value. To meet the entry criteria, subjects must demonstrate an FEV_1 of ≥45% and ≤85% of predicted normal. Those who fail to meet this

criterion may present for repeat spirometry testing within 7 days.

Subjects who demonstrate an FEV_1 of ≥45% and ≤85% of predicted normal will then be administered albuterol 360 µg delivered via a pMDI with a spacer. The reversibility of FEV_1 will be assessed with a second spirometry assessment 30 minutes (±5 minutes) later. To meet the entry criteria, subjects must demonstrate ≥15% reversibility of FEV_1 (reversibility of 14.50% to 14.99% will be rounded to 15%) and a ≥0.2 L increase within 30 minutes (±5 minutes) following the administration of 360 µg albuterol delivered via a pMDI. Subjects who demonstrate reversibility of FEV_1 ≥10% and <14.5% or those who fail to show an increase of >0.20 L within 30 minutes (±5 minutes) of 360 µg albuterol may present for repeat spirometry and reversibility testing within 7 days.

xxxxx

At the baseline visit on Day 1 (following the run-in period), the subjects will have a predose (30 minutes before initial dosing) spirometry assessment, have a time point 0 spirometry assessment (which will be averaged with the first spirometry assessment for a baseline value), receive their first morning dose of study medication, and have subsequent serial spirometry assessments as follows: 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours after dosing. A window of ±5 minutes will be applied through the 3-hour assessment, and a window of ±10 minutes will be applied for the assessments at Hours 4 through 12.

If a subject requires rescue medication during the postdose serial spirometry assessment period of the baseline visit, the event will be recorded as an AE and the medication used will be recorded as a concomitant medication in the eCRF; the date and time of administration as well as the number of puffs will be recorded. These subjects may continue in the study.

At the end-of-treatment visit, subjects will have 2 spirometry assessments. Study medication must not have been taken within 12 hours (±2 hours) and rescue medication must not have been taken within 6 hours of the first spirometry assessment. The first spirometry assessment will be conducted at the same time of day (±1 hour) as the first predose baseline spirometry assessment (ie, 30 minutes before initial dosing), and the second spirometry assessment will be performed 30 minutes (±5 minutes) later; the end-of-treatment FEV_1 value will be the average of the 2 assessments.

6.2 Safety Assessments

Safety assessments in this study include evaluation of all AEs noted during study participation (including exacerbation of preexisting conditions), changes in concomitant medication during study participation (including change in dose), and changes from baseline in vital signs.

4.1.1 Handheld Device for Home Use

At the screening visit, subjects will be provided with and trained on the proper use of the handheld device that will xxx collect diary information. Subjects will be asked to xxx answer diary questions twice daily (at home), in the morning and in the evening, approximately 12 hours apart. xxxxx

Diary information collected may include, but is not limited to, the following:

- xxxxx
- Time of dosing of study medication in the morning and canister used (ie, Canister 1 or Canister 2).
- Time of dosing of study medication in the evening and canister used (ie, Canister 1 or Canister 2).
- xxxxx

In addition, subjects will be asked to indicate if any AEs or changes in concomitant medications occurred.

Study center personnel will review the data xxx. Study medication, diary, and compliance re-education will be provided as needed. xxxxx

Data from the handheld device will not be electronically entered into the analysis database or statistically analyzed. xxxxx

6.2.1 Asthma Exacerbation

Alert criteria for individual subjects with worsening asthma have been designed to ensure subject safety. If any of the following criteria are met, the subject will be instructed to come into the study center for evaluation so that the investigator can determine whether the subject's overall clinical picture is consistent with worsening asthma or if the subject will be

withdrawn from the study:

- xxxxx
- The subject experiences any of the following during a 7-day period:
    - Three or more days in which 12 or more inhalations per day of rescue medication were used
    - Three or more nights in which the subject was awoken with nighttime asthma exacerbation requiring rescue medication
    - Persistent worsening of asthma symptoms

Clinical asthma exacerbation: Subjects who do not meet the alert criteria but who experience a clinically meaningful worsening of their asthma warranting a change in their asthma treatment will be removed from the study. The investigator should offer alternative treatment consistent with the policies and procedures at the study center. xxxxx

6.2.2 Adverse Events

6.2.3.1 Definitions of Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study medication or their clinical significance.

An AE is defined as any untoward medical occurrence in a subject that is associated with the use of a study medication in humans, whether or not considered related to the study medication. Subjects will be instructed to contact the investigator at any time after randomization if any symptoms develop.

A treatment-emergent AE is defined as any event not present before exposure to study medication or any event already present that worsens in either intensity or frequency after exposure to study medication.

A life-threatening AE or life-threatening suspected adverse reaction is defined as an event that, in the view of the investigator or the sponsor, places the subject at immediate risk of death; it does not include an event that had it occurred in a more severe form might have caused death.

An SAE or serious suspected adverse reaction is defined as any event that, in the view of the investigator or the sponsor, results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Suspected adverse reaction means any AE for which there is a reasonable possibility that the study medication caused the AE. For the purposes of FDA safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the study medication and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by the study medication.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator’s brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator’s brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator’s brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator’s brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator’s brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

6.2.3.2 Eliciting and Documenting Adverse Events

Adverse events will be assessed beginning at enrollment (date of signed informed consent) and up to the end-of-treatment visit. Even though the Investigator does not need to actively

monitor subjects for AEs once the study has ended, SAEs occurring to a subject within 30 days after the last dose of study medication should be reported if the Investigator becomes aware of them.

At each visit, subjects will be asked a standard nonleading question (such as "How have you felt since your last visit") to elicit any medically related changes in their well-being. They will also be asked if they have visited an emergency room/urgent care clinic or have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (see Section 6.2.4).

In addition to subject observations, AEs identified from any study data (eg, vital sign data, laboratory values, physical examination findings) or identified from review of other documents (eg, subject diaries) that are relevant to subject safety will be documented on the AE page in the eCRF.

6.2.3.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF. Information to be collected includes date of onset, description of AE, investigator-specified severity and relationship to study medication, action taken, and date of resolution. Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed up to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate will not be reported as an AE. However, if it deteriorates at any time during the study, it will be recorded as an AE.

Any AE that meets SAE criteria (Section 6.2.3.1) must be **immediately** (ie, within 24 hours after the time study center personnel first learn about the event) reported on the SAE page in the eCRF. The 24-hour safety hotline telephone number and the SAE fax number are located on the cover page.

6.2.3.4 Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the subject's

daily activities. The intensity of the AE will be rated as mild, moderate, or severe using the following criteria:

Mild: These events require minimal or no treatment and do not interfere with the subject's daily activities.

Moderate: These events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with normal functioning.

Severe: These events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

6.2.3.5 Assessment of Causality

The investigator's assessment of an AE's relationship to study medication is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the test article in causing or contributing to the AE will be characterized using the following classification and criteria:

Unrelated: This relationship suggests that there is no association between the study medication and the reported event.

Possible: This relationship suggests that treatment with the study medication caused or contributed to the AE, ie, the event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the study medication, but could also have been produced by other factors.

Probable: This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the study medication seems likely. The event disappears or decreases on cessation or reduction of the dose of study

medication.

Definite: This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

6.2.3.6 Follow-Up of Subjects Reporting Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF.

For SAEs, follow-up information to an initial safety report must be provided by the Investigator as soon as the relevant information is available. Relevant information such as discharge summaries, autopsy reports, and medical consultations will be reviewed in detail by the Investigator and discussed with the medical monitor as appropriate.

All SAEs or AEs that lead to discontinuation of study medication will be followed up until satisfactory resolution, the investigator deems the event to be chronic or not clinically significant, or the subject is considered to be stable.

6.2.3 Concomitant Medications

Use of all concomitant medications will be recorded in the subject's eCRF. The minimum requirement is that the drug name, dose, and dates of administration are to be recorded (start and stop dates). This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Any changes in concomitant medications (including discontinuations of drugs, changes in dose, and initiation of new medications) will also be recorded in the subject's eCRF.

The run-in period will be used to washout prestudy medications and to establish FEV_1 baseline values. See Appendix 1 for a complete list of washout medications and the required washout period for each; these medications are excluded throughout the study unless otherwise noted. Throughout the study, any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding the medication, and as necessary withdrawal (see Section 4.2), are recorded in full in the eCRF.

6.2.4 Physical Examination and Vital Signs

A complete physical examination, including height and weight, will be performed at the screening visit and the end-of-treatment visit; height only needs to be collected at the screening visit. Vital sign assessments, including blood pressure and heart rate, will be collected at screening, baseline, and at the end-of-treatment visits.

All data collected from the physical examinations and vital sign assessments must be available in the source documents but will not be added to the analysis database. An abnormal vital sign value or physical examination finding at the screening visit will be captured in the medical history. An abnormal vital sign value or physical examination finding at the end-of-treatment visit that has worsened since the screening visit will be captured as an AE.

6.2.5 Electrocardiogram

A standard 12-lead electrocardiogram assessment will be performed locally at the study center during the screening visit and following standard procedures at the study center. If spirometry has been performed, the subject should rest for at least 10 minutes prior to the electrocardiogram assessment. Data collected from the electrocardiogram assessments must be available in the source documents but will not be added to the analysis database.

6.3 Laboratory Analyses

Laboratory testing will be performed at local laboratories only at the screening and end-of-treatment visits. Laboratory assessments will be obtained per standard of care at each study center, with the laboratory assessments in Table 6–1 collected at a minimum. The volume of blood drawn throughout the study will vary based on each study center's standard of care but is expected to be approximately 50 mL per subject during the course of the study. Additional blood draws may be needed if clinically indicated, as determined by the investigator.

Any data collected from the laboratory testing must be available in the source documents but will not be added to the analysis database. An abnormal laboratory value at the screening visit will be captured in the medical history. An abnormal laboratory value at the end-of-treatment visit that has worsened since the screening visit will be captured as an AE.

A urine pregnancy test will be used at the screening and baseline visits to screen potential subjects for eligibility to participate in the study. A serum pregnancy test must be obtained at the screening and end-of-treatment visits. If a pregnancy occurs, refer to Section 6.4.

Table 6–1 Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin	Urea	pH	Hepatitis B (Screening only)
Hematocrit	Creatinine	Glucose (qualitative)	Hepatitis C (Screening only)
RBC count	Glucose	Protein (qualitative)	Human immunodeficiency
Platelet count	Calcium	Blood (qualitative)	virus (Screening only)
WBC count	Sodium	Ketones	Pregnancy test (urine and/or
Total neutrophils	Potassium	Nitrites	serum)
(absolute)	Chloride	Leukocyte esterase	
Eosinophils (absolute)	Total CO_2 (bicarbonate)		
Monocytes (absolute)	Alanine aminotransferase		
Basophils (absolute)	Aspartate aminotransferase		
Lymphocytes (absolute)	Total bilirubin		
	Alkaline phosphatase		
	Uric acid		
	Albumin		
	Total protein		

6.4 Pregnancy

Subjects who become pregnant during the study will be withdrawn as outlined in Section 4.2.

Pregnancy is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during study participation must be reported in the eCRF. To ensure subject safety, each pregnancy must be reported to 3M or its designee within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine the outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the subject was discontinued from the study. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriages must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study medication must be promptly reported to 3M or its designee.

7 Statistical Considerations

Detailed methodologies for the summary and statistical analyses of the data collected in this study will be documented in a separate document, the statistical analysis plan (SAP). The SAP may modify the statistical plans outlined in this protocol; however, major modifications of the primary endpoint definition and/or its analyses will also be reflected in a protocol amendment.

7.1 Endpoints

7.1.1 Primary Efficacy Endpoints

The primary efficacy endpoints are as follows:

- Change from baseline in FEV_1AUC_{0-12} at Day 1

  FEV_1 will be measured on Day 1 before dosing (30 minutes before initial dosing), at time point 0, and 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours after dosing for the calculation of FEV_1AUC_{0-12}. Details on the calculations of this endpoint will be provided in the SAP.

- Change from baseline to the end-of-treatment in FEV_1

  The baseline FEV_1 is defined as the average of the 2 predose FEV_1 values measured in the morning of the first day of treatment. The end-of-treatment FEV_1 is defined as the average of the 2 FEV_1 values measured in the morning on the last day of treatment and within 1 hour of the first predose assessment on the first day of treatment.

7.1.2 Safety Endpoint

Safety will be evaluated by assessing number (percent), severity, and relatedness of AEs and SAEs between treatment groups.

7.2 Sample Size Calculations

Approximately 1470 adult subjects (18 years of age or older) with asthma are proposed to be randomized to the 3 treatment groups in a 3:3:1 ratio (630 subjects per active treatment group and 210 in the placebo group).

7.2.1 Equivalence

xxxxx. Sample size calculations are mainly driven by demonstrating equivalence for the change from baseline in FEV_1 at Week 6. Equivalence will be defined as the 90% CIs for the ratio (test/reference) falling within the (0.80, 1.25) target ratio. The sample size of 567 subjects in each active treatment group will provide approximately 87.1% power at the 5% significance level for the equivalence test of means using two 1-sided tests and assuming a true ratio of the means equal to 0.95, coefficient of variance (CV) of 1.00, and equivalence limits of the mean ratio of 0.80 and 1.25.

Similarly for the change from baseline in FEV_1AUC_{0-12} at Day 1 endpoint, using an SD of xxx the sample size of 567 subjects in each active treatment group will provide 90.1% power at the 5% significance level for the equivalence test of means using two 1-sided tests and assuming a true ratio of the means equal to 0.95, CV of 0.95, and equivalence limits of the mean ratio of 0.80 and 1.25.

The sample size will be based on the per-protocol set (PPS). Therefore, accounting for an approximate 10% dropout rate from the PPS, a sample size of 1470 subjects (630 subjects per active treatment group and 210 in the placebo group) is proposed.

Sample size calculations were performed xxx

7.2.2 Superiority

xxxxx For the change from baseline in FEV_1, the sample size of 630 in the active treatment group and 210 subjects in the placebo group will provide more than 99% power to reject the hypothesis of equal means at the 5% significance level using a 2-sided 2-sample equal-variance *t* test, assuming that the population mean difference xxx

Similarly, for FEV_1AUC_{0-12}, the sample size of 630 in the active treatment group and 210 subjects in the placebo group will provide more than 99% power to reject the hypothesis of equal means at the 5% significance level using a 2-sided 2-sample equal-variance *t* test and using the population mean difference xxx for both treatments.

Power was calculated using xxx for a 2-sample *t* test assuming equal variance. xxxxx

7.3 Analysis Sets

The following analysis sets will be used in the statistical analyses:

Full-analysis set (FAS): The FAS will consist of all subjects who were randomly assigned to receive single-blind study medication. All analyses using the FAS will group subjects according to randomized treatment. This analysis set will be used to assess the assay sensitivity of each active treatment (3M Inhaler and Symbicort Reference Inhaler) compared with placebo.

Per-protocol set (PPS): The PPS will consist of all FAS subjects who fulfill all inclusion/exclusion criteria, are compliant to the study medication schedule (see Section 5.7), have not taken any prohibited medications, and have no significant protocol deviations.

Per definition, the PPS will only include subjects who received the study medication to which they were randomly assigned. This analysis set will be used to assess the therapeutic equivalence of 3M Inhaler compared with Symbicort Reference Inhaler.

Safety set: The safety set will consist of all subjects who received any study medication. All analyses using the safety set will group subjects according to treatment actually received. All safety endpoints will be analyzed based on the safety set.

7.4 Description of Subgroups to be Analyzed

No subgroup analyses are planned.

7.5 Statistical Analysis Methodology

Statistical analysis will be performed using SAS software Version 9.2 or later.

Summary statistics of the data collected will be provided by treatment (3M Inhaler, Symbicort Reference Inhaler, and placebo). Continuous variables will be summarized using the mean, SD, CV, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages.

Details of the statistical analyses, methods, and data conventions will be further described in the SAP.

7.5.1 Analysis of Primary Efficacy Endpoint

In order to claim therapeutic (overall) equivalence of the 3M Inhaler and the Symbicort Reference Inhaler, the following results should be demonstrated for both primary endpoints:

- Equivalence of the active treatments means using ratio. The 90% CI for the ratio should fall within 80.00% and 125.00%
- Assay sensitivity of each active treatment compared with placebo will be established if both active treatment groups are statistically superior to placebo (P<0.05)

7.5.1.1 Equivalence

For each primary endpoint, the equivalence analysis of 3M Inhaler compared with the Symbicort Reference Inhaler will be performed using an analysis of covariance. Factors will be treatment (3M Inhaler and Symbicort Reference Inhaler) and the appropriate baseline for the endpoint. From the least-squares (LS) mean estimates obtained for each treatment group, the ratio (3M Inhaler/Symbicort Reference Inhaler) will be calculated. Fieller's theorem [Hirschberg, 2010] will then be used to generate 2-sided CIs for each ratio. This analysis will be based on the PPS.

The mean of the 2 predose FEV_1 measurements taken at Day 1 will be used as the baseline for the $FEV_1AUC_{0\text{-}12}$ assessment.

The baseline for the FEV_1 endpoint will be calculated by taking the mean of the 2 predose FEV_1 measurements taken at the baseline visit (Day 1).

The first FEV_1 assessment on the last day of the 6-week treatment period should correspond to the same time of day as that used for the baseline measurements (see Section 6.1).

The 90% CI for the 2 active treatments (3M Inhaler and Symbicort Reference Inhaler) for the primary endpoint should fall within the limits of 80.00% to 125.00% for equivalence to be concluded [FDA, 2015].

7.5.1.2 Superiority

Assay sensitivity will be shown if the 3M Inhaler and Symbicort Reference Inhaler are both statistically superior to placebo (P<0.05) with regards to both study primary endpoints.

For the superiority test, the analysis will be performed using an analysis of covariance model fitted to each primary endpoint. Treatment (3M Inhaler, Symbicort Reference Inhaler, and placebo) will be included as a fixed effect. Baseline FEV_1 will also be included as a continuous covariate (using the definition appropriate for each endpoint). The LS means will be derived for each treatment, and LS mean differences will be calculated by comparing each active treatment group (3M Inhaler and Symbicort Reference Inhaler) with placebo for each primary endpoint. Standard errors and 2-sided 95% CIs will be calculated for LS means and LS mean differences. In addition, 2-sided *P* values will be presented for the LS mean differences. The superiority of each active treatment compared with placebo will have been demonstrated if the *P* value for the pairwise comparison is statistically significant at the 5% level.

Assay sensitivity will be achieved if both pairwise comparisons (3M Inhaler compared with Symbicort Reference Inhaler compared with placebo) are statistically significant at the $P<0.05$ significance level for both primary endpoints.

No adjustment for multiplicity is required because the primary endpoints are expected to be highly correlated and because equivalence on the basis of both endpoints is required before equivalence of the 2 inhalers can be claimed.

These analyses will be based on the FAS.

Additional sensitivity analyses may be carried out as described in the SAP, as appropriate, which may include accounting for FEV_1 missing values in the FAS.

7.5.2 Safety Analyses

All AEs will be reported, whether or not they are considered to be related to the treatment. The report of each AE will include date of onset, description of AE, investigator-specified severity and relationship to study medication, action taken, and date of resolution. This information will assist in determining whether the incidence and severity of adverse reactions are different among the 3 treatment groups.

7.5.3 Other Analyses

Summary statistical analyses will be provided for demographics, medical history, risk factor variables at baseline, and study medication compliance.

7.5.4 Blinded Sample Size Re-estimation

A blinded sample size re-estimation may be performed after 30% of the subjects are enrolled to check for the sample size assumptions and, if necessary, increase the sample size. However, if a sample size re-estimation was to be performed, details would be prespecified in a protocol amendment prior to any statistical analysis of the data.

7.5.5 Interim Analysis

There is no interim analysis planned for this study. However, if an interim analysis was to be performed, details would be prespecified in a protocol amendment prior to any statistical analysis of the data.

7.6 Data Quality Assurance

Data will be entered into an electronic data capture system. Management of clinical data will be performed in accordance with applicable 3M or its designee's standards and data cleaning procedures to ensure the integrity of the data (eg, removing errors and inconsistencies in the data).

7.6.1 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents include but are not limited to diary cards, laboratory reports, physical examination records, and spirometry assessments.

Study center personnel will enter subject data into eCRFs. The analysis data sets will be a combination of these data and data from other sources (eg, spirometry data).

Clinical data management will be performed in accordance with applicable 3M or its designee's standards and data cleaning procedures to ensure the integrity of the data, eg, removing errors and inconsistencies in the data. Adverse events and concomitant medication terms will be coded using MedDRA.

8 Ethics

8.1 Independent Ethics Committee or Institutional Review Board

Federal regulations and the International Council for Harmonisation (ICH) guidelines require that approval be obtained from an institutional review board (IRB) before participation of human subjects in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject or the subject's legal guardian must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with ICH harmonised tripartite guideline E6: Good Clinical Practice (GCP) will be maintained by the study center and will be available for review by the sponsor or its designee.

All IRB approvals should be signed by the IRB chairman or designee and must identify the IRB name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB. The investigator must promptly supply the sponsor or its designee, the IRB, and where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

8.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations.

If a serious breach is detected, the sponsor or its designee will take appropriate corrective and preventative actions in response. These actions will be documented and the FDA will be notified as appropriate.

The investigator is responsible to take appropriate action to protect a subject's life but must notify the sponsor or its designee and the medical monitor after any such event.

3M or its designee will comply with all FDA requirements when reporting SAEs and urgent

safety issues.

8.3 Subject Information and Consent

A written informed consent in compliance with US Title 21 Code of Federal Regulations (CFR) Part 50 shall be obtained from each subject before entering the study or performing any unusual or nonroutine procedure that involves risk to the subject. An informed consent template may be provided by the sponsor or its designee to the study center. If any institution-specific modifications to study-related procedures are proposed or made by the study center, the consent should be reviewed by the sponsor or its designee or both before IRB submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating subjects must sign the revised form.

Before recruitment and enrollment, each prospective subject or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the subject or legal guardian understands the implications of participating in the study, the subject or legal guardian will be asked to give consent to participate in the study by signing the ICF.

The investigator shall retain the signed original ICF and give a copy of the signed original form to the subject or legal guardian.

9 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB but will not result in protocol amendments.

9.1 Confidentiality

All evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, the FDA, or the IRB.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

9.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor or its designee to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide to the sponsor or its designee a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.

The sponsor or its designee are not financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, the sponsor or its designee are not financially responsible for further treatment of the subject's disease.

9.3 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R1) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to the following:

- IRB approval
- Original investigator-signed investigator agreement page of the protocol
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- Curriculum vitae for the investigator and each subinvestigator listed on Form FDA 1572
- Financial disclosure information to allow the sponsor or its designee to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to the sponsor or its designee a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study
- IRB-approved informed consent, samples of study center advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject or legal guardian
- Laboratory certifications and normal ranges for any local laboratories used by the study center, in accordance with 42 CFR 493

9.4 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6. The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

9.5 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6 and all applicable guidelines and regulations.

9.6 Adverse Events and Study Report Requirements

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in the protocol (see Section 6.2.3.3 and Section 6.2.3.6). In addition, the investigator agrees to submit annual reports to the study center's IRB as appropriate.

9.7 Investigator's Final Report

Upon completion of the study, the investigator, or where applicable the institution, should provide the IRB with a summary of the study's outcome at the study center (eg, total number of subjects enrolled, study duration) and provide the sponsor or its designee with any reports required.

9.8 Records Retention

xxxxx

9.9 Publications

xxxxx

10 Study Management

10.1 Monitoring

10.1.1 Monitoring of the Study

The clinical monitor, as a representative of the sponsor or its designee, has the obligation to follow the study closely. In doing so, the monitor will visit the investigator and study center at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and study center personnel.

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

10.1.2 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency (eg, FDA or other regulatory agency) access to all study records.

The investigator should promptly notify the sponsor or its designee of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor or its designee.

10.2 Management of Protocol Amendments and Deviations

10.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject, must be reviewed and approved by the sponsor or its

designee. Amendments to the protocol must be submitted in writing to the investigator's IRB for approval before subjects can be enrolled into an amended protocol.

10.2.2 Protocol Deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study subjects without prior IRB approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB for review and approval, to the sponsor or its designee for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor or its designee and the IRB and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the subject or investigator that results in a significant, additional risk to the subject. Significant deviations can include nonadherence to inclusion or exclusion criteria, enrollment of the subject without prior sponsor approval, or nonadherence to FDA regulations or ICH GCP guidelines, and will lead to the subject being withdrawn from the study (Section 4.2).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Investigators will be notified in writing by the monitor of deviations. The IRB should be notified of all protocol deviations in a timely manner.

10.3 Study Termination

Although 3M has every intention of completing the study, 3M reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last subject completes the last visit (ie, end-of-treatment visit or follow-up visit for subjects who have an SAE or those who withdraw due to an AE).

10.4 Final Report

Whether the study is completed or prematurely terminated, the sponsor or its designee will

ensure that the clinical study reports are prepared and provided to the regulatory agency as required by the applicable regulatory requirements. The sponsor or its designee will also ensure that the clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study report, the sponsor or its designee will provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate. The study results will be posted on publicly available clinical trial registers.

11 References

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12 Appendices

12.1 Appendix 1: Allowed and Disallowed Medications

All medications used in the treatment of asthma (inhaled corticosteroids, long-acting β agonists, noncorticosteroids) are to be discontinued at the screening visit. The subject will be supplied with a short-acting β2 agonist (SABA) for use to relieve asthma symptoms as required during the entire study (see Section 5.2.2). The subject's routine SABA will be discontinued at the screening visit.

The following drugs are prohibited or restricted during the study:

12.2 Appendix 2: Contraception

12.2.1 Females of Non-childbearing Potential

Female subjects of non-childbearing potential must meet and have documentation of at least one of the following criteria:

- xxxxx
- Postmenopausal, defined as amenorrheic for at least 2 years OR have been amenorrheic for less than 2 years but have a serum follicle-stimulating hormone level >30 IU/L in the absence of hormone replacement therapy
- Surgically sterile, which includes hysterectomy or bilateral oophorectomy

All other females will be considered to be of childbearing potential.

12.2.2 Females of Childbearing Potential

Female subjects of childbearing potential must use an acceptable method of contraception starting from the screening visit through the end-of-treatment visit.

xxxxx

12.3 Protocol Amendments

12.3.1 Protocol Amendment 1 Summary of Changes

The original protocol was amended to provide additional clarity around the baseline spirometry testing and exclusion criterion #9.

Following is a summary of the changes. Additions are indicated in bold and underlined font, and deletions are indicated using strikethrough text.

Global Change

Reference to the protocol was changed from “Original Protocol” to “Protocol Amendment 1” and the date was changed to 31 Oct 2016.

Exclusion Criteria #9:

Has a current diagnosis or history of hepatitis B, hepatitis C, **or** human immunodeficiency virus **as determined by laboratory testing at Screening**, or **active** tuberculosis **as determined by medical history and physical examination**

6.1 Efficacy Assessments

At the screening visit, subjects will have 2 spirometry assessments. The screening assessments will be completed in the morning. The first spirometry assessment will be conducted to assess the subject's FEV_1 value. To meet the entry criteria, subjects must demonstrate an FEV_1 of ≥45% and ≤85% of predicted normal. **Those who fail to meet this criterion may present for repeat spirometry testing within 7 days.**

Subjects **who demonstrate an FEV_1 of >45% and <85% of predicted normal** will then be administered albuterol 360 µg delivered via a pMDI with a spacer. The reversibility of FEV_1 will be assessed with a second spirometry assessment 30 minutes (±5 minutes) later. To meet the entry criteria, subjects must demonstrate ≥15% reversibility of FEV_1 (reversibility of 14.50% to 14.99% will be rounded to 15%) and a ≥0.2 L increase within 30 minutes **(±5 minutes)** following the administration of 360 µg albuterol delivered via a pMDI. Subjects who demonstrate reversibility of FEV_1 ≥10% **and** <14.5% or those who fail to how an increase of >0.20 L within 30 minutes **(±5 minutes)** of 360 µg albuterol may present for repeat spirometry and reversibility testing **within** 7 days.

The repeat spirometry assessment must be conducted at the same time of day (±1 hour) as the original screening assessment. Subjects who meet the spirometry requirements upon repeat testing can enter the run-in period (provided they meet all other inclusion criteria and none of the exclusion criteria). Subjects who required repeat spirometry testing will have the baseline visit **up to** 21 days after the initial screening visit (versus approximately 14 days after the initial screening visit for subjects who do not require repeat testing). **If the subject fails to meet all of the spirometry assessment criteria outlined in the inclusion criteria (see Section 4.1.1)** upon repeat testing, the subject will be considered to have failed screening.

Table 6-1 Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin	Urea	pH	Hepatitis B (Screening only)
Hematocrit	Creatinine	Glucose (qualitative)	Hepatitis C (Screening only)
RBC count	Glucose	Protein (qualitative)	Human immunodeficiency
Platelet count	Calcium	Blood (qualitative)	virus (Screening only)
WBC count	Sodium	Ketones	~~Tuberculosis (Screening~~
Total neutrophils	Potassium	Nitrites	~~only)~~
(absolute)	Chloride	Leukocyte esterase	Pregnancy test (urine and/or
Eosinophils (absolute)	Total CO_2 (bicarbonate)		serum)
Monocytes (absolute)	Alanine aminotransferase		
Basophils (absolute)	Aspartate aminotransferase		
Lymphocytes (absolute)	Total bilirubin		
	Alkaline phosphatase		
	Uric acid		
	Albumin		
	Total protein		