RETHINC: REdefining Early THerapy IN COPD

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RETHINC: REdefining Therapy IN early COPD

VERSION 4.2

Study Sponsor(s): National Institutes of Health

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INVESTIGATOR SIGNATURE PAGE	
Protocol:	**Version/Date:**
Site Principal Investigator *(Each site investigator must complete a signature page)*: *[Insert na*	
Title: RETHINC: REdefining Therapy IN early COPD	
Study Sponsor: National Institutes of Health	
INSTRUCTIONS: *The site Principal Investigator should print, sign, and date at the indicated location below. A copy should be kept for your records and the original signature page sent. After signature, please return the original of this form by surface mail to:* ***[Insert Name/Title and Address]***	
I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 45 CFR part 46 and 21 CFR parts 50, 56, and 312, and in the International Conference on Harmonization (ICH) document *Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance* dated April 1996. Further, I will conduct the study in keeping with local legal and regulatory requirements. As the site Principal Investigator, I agree to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without the written permission of the Data Coordinating Center, the Protocol Chairs and the IRB. _____ **Site Principal Investigator (Print)** _____ _____ **Site Principal Investigator (Signature)** **Date**	

Summary of Amendment #4 changes

Protocol Version	Page* #	Location	Revision, Insertions, Deletions	Rationale for Change
4.2	36	**Schedule of Events for Participants Requiring Washout**	Clarified washout for 30 days or more instead of <-4 week period.	Administrative change
4.1	11, 24, 25	Protocol Synopsis, Study Hypothesis/ Objectives, Study Design	Addition of a secondary endpoint: improvement in both BDI/TDI and SGRQ	Improvement in both metrics is clinically meaningful and well powered.
4.0 (2/2018)	p. 1, TOC and footers	N/A	Updated protocol number and date and page numbers.	Administrative change.
4.0 (2/2018)	p. 11 and 26	Protocol Synopsis and Selection of Participants and Clinical sites	Reduce smoking pack years required for enrollment from 20 to 10.	The original protocol was based on preliminary data generated from the SPIROMICS trial (NEJM 2016; 374:1811) where we demonstrated a high rate of respiratory exacerbations and CT airway wall thickening among individuals with CAT≥10 and smoking history ≥ 20 pack years but normal spirometry. Twenty pack years was an inclusion criteria for Spiromics. Our

				hypothesis is that these individuals have airways disease not detectable by spirometry but responsive to a bronchodilator. Since then, data published by Dr. Wedzicha in AJRCCM demonstrates that at a threshold of ≥10 pack-years smoking history, respiratory symptoms begin to increase and lung function starts to decline suggesting airway pathology begins at this smoking threshold (AJRCCM 2017;196:1021 & AJRCCM 2016;193:662). Further, subgroup analyses of the COPDGene cohort (similar to SPIROMICS but different inclusion criteria) isolating to subjects with 10-20 pack years smoking history demonstrates similar statistically significant elevations in exacerbation rates and CT airway wall thickening in symptomatic GOLD 0 subjects as was seen in the SPIROMICS NEJM publication. These data support that a 10 pack year smoking history will be sufficient to identify the patient population of interest.
4 (2/2018)	p. 15, 27 and 30	Protocol Synopsis, Study Hypothesis and Exclusion Criteria	Reduce FVC requirement from 80% to 70% predicted	Our choice to exclude patients with FVC<80% was based on inclusion criteria for the SPIROMICS study. Our goal was to exclude patients with other significant lung diseases, however we

				have found that the use of 80% is overly strict and excluding some patients, for instance, who are overweight. In secondary analyses of the COPDGene cohort (similar to SPIROMICS but different inclusion criteria), isolating to subjects with FVC between 70-80% predicted demonstrates similar statistically significant elevations in exacerbation rates and CT airway wall thickening in symptomatic GOLD 0 subjects as was seen in the SPIROMICS NEJM publication. Therefore we propose to drop to 70% which we feel is still adequate to exclude significant interstitial lung disease.
4/2018	p. 31	Table 4.3-1	Ease restrictions on prohibited medications	Our original prohibited medications list was based on the FLIGHT 1 and 2 study protocol documents provided to us by Novartis. FLIGHT 1 and 2 were performed in order to obtain FDA approval for our study drug (Utibron: indacaterol/glycopyrrolate) in a COPD patient population. Since the protocol was written, however, the drug was approved by the FDA and the package insert with guidance regarding drug interactions is now available. Several of the drugs prohibited by the Novartis studies are no longer included in the

				package insert. These include anti-psychotics, varenicline, mast cell stabilizers, and leukotriene antagonists. None of these medications are listed on the Utibron package insert and therefore allowing such medications should not increase risk for participants, but should improve our ability to recruit. We already have restrictions in place in the protocol to exclude patients who would not be appropriate for the study such as active psychosis or asthma and therefore do not believe that easing these restrictions will result in inclusion of patients inappropriate for the study.
4/2018	p. 35-37 and p. 38-39	Screening/ Enrollment and Schedule of events	Reduce post-BD time from 30 minutes to 15 minutes	The choice of 30 minutes was based on the SPIROMICS protocol which also included administration of an anti-cholinergic. However, here we are using albuterol alone. We note that the other PTC studies are using 15 minutes and therefore we propose to change this to reduce coordinator confusion and conform to the other PTC studies. The ATS/ERS task force on standardization of spirometry (ERJ 2005;26:319) recommends 15 minutes for bronchodilator testing after a short-acting beta agonist.

4/2018	p.29	Survey Instruments to be Used	Clarified name of test as "BDI/TDI" as opposed to just "TDI"	Clarification to reduce confusion
4/2018	p.29	Stratification, Randomization, and Blinding/Masking	Clarified text regarding drug resupply as this process has been modified since the protocol was written.	Clarification to clarify process
4/2018	p. 30	Securing Blinding and Randomization	Clarified text regarding blinding and randomization	Clarify process
4/2018	p. 31	Table 4.3-2	Clarified title of Table 4.3-2 from "Prohibited COPD-related Medications" to "Prohibited COPD-related Medications Requiring Washout Period of 30 days"	Clarify that prohibited medications can be washed out
4/2018	p. 35-39	Pre-Screening and Screening/ Enrollment	Updated details regarding how to screen, schedule of events for bringing subjects in who require washout, and clarification of the rescreening process	Increased detail provided in protocol
4/2018	p. 40	Visit Windows	Added that if a delay in Visit 2 causes subject to run out of study drug, study site should contact DCC for further instructions to determine whether drug supply would allow more drug to be dispensed.	Process clarification
4/2018	p.41	Special consideration for treatment failure subjects	Provided enhanced detail regarding pulmonary function testing to be performed on treatment failure subjects.	Process clarification

Summary of Amendment #3 changes

3.0 (09/2017)	p. 27, 28	7.5 & 7.6 – Schedule of Events for both Non-Washout and Washout Participants	*New Text:* **Baseline Medical History** *Previous Text:* Medical History	Clarification of which medical history information is being collected.
3.0 (09/2017)	p. 27, 28	7.5 & 7.6 Schedule of Events for both Non-Washout and Washout Participants	*New Text:* **FEV1, FVC, SVC and IC before administration of study drug and FEV1 and FVC every hour after administration of study drug for a total of three hours (i.e. a trough and an AUC_{0-3} measurement).** *Previous Text:* FEV1, FVC, SVC and IC before and every hour after administration of study drug for three hours (i.e. a trough and an AUC_{0-3} measurement).	Consistency in description of AUC_{0-3} process throughout protocol.
3.0 (09/2017)	p. 27, 28	7.5 & 7.6 – Schedule of Events for both Non-Washout and Washout Participants	Addition of footnote and corresponding superscript "**End of Study[3]**": "3. Should a subject terminate early, the subject will be brought in to complete all assessments included at the Week 12 End of Study visit."	Clarification of process to follow for subjects who terminate early from the study.
3.0 (09/2017)	p. 30	7.9 Discontinuation of study treatments	Addition of 'Discretion of site primary investigator' to circumstances for study treatment discontinuation	Confirmation that site investigator may discontinue patients per their discretion.
3.0 (09/2017)	p. 30	7.9.1 Special Considerations for	Added section to provide specific instructions on drug discontinuation for subjects who meet treatment failure endpoint.	Provide clarification on how to handle a subset of study participants who may

		Treatment Failure Subjects		have a specific experience during study participation.
3.0 (09/2017)	p. 31	7.9.2 Special Considerations for subjects who start a prohibited medication	Added section to provide specific instructions for subjects who begin using prohibited medication during the course of their participation in the study.	Provide clarification on how to handle a subset of study participants who may have a specific experience during study participation.
3.0 (09/2017)	p. 31	7.9.3 Special Considerations for subjects who experience an AE/SAE requiring study drug interruption	Added section to provide specific instructions for subjects who experience a safety event requiring drug interruption	Provide clarification on how to handle a subset of study participants who may have a specific experience during study participation.
3.0 (09/2017)	p. 32	8.2.3 Serious Adverse Event (SAE)	Removed previous definitions of SAE to align with those of the PTC.	Consistency between PTC and PLG in regards to safety reporting.
3.0 (09/2017)	p. 34	8.3.2 Attribution of Adverse Events	Modified entire table to align with PTC.	Consistency between PTC and PLG in regards to safety reporting.
3.0 (09/2017)	p.35	8.5.2 Reporting to Health Authority	*New Text:* **After an adverse event requiring 24 hour reporting (per Section 8.5.1, *Reporting of Serious Adverse Events*), the event will be submitted by the site investigator and assessed by protocol chairs and the DCC per local regulations. Although this protocol was submitted to the FDA and received an IND exemption, MedWatch forms will be completed**	Addition of additional reporting for the DCC to Sunovion Pharmaceuticals.

			for applicable Serious Adverse Events and forwarded to Sunovion Pharmaceuticals (global oversight for the study) for further reporting to the FDA. *Previous Text:* After an adverse event requiring 24 hour reporting (per Section 8.5.1, *Reporting of Serious Adverse Events*), the event will be submitted by the site investigator and assessed by protocol chairs and the DCC per local regulations. This protocol was submitted to the FDA and received an IND exemption.	

Protocol Synopsis

Title	Redefining Therapy in early COPD: RETHINC
Short Title	RETHINC
Clinical Phase	Phase III
Study Objectives	A 12-week multicenter, randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy and safety of indacaterol/glycopyrrolate 27.5/15.6 mcg inhaled twice daily in symptomatic current and former smokers with respiratory symptoms despite preserved spirometry as defined by CAT ≥ 10 and post-bronchodilator FEV_1/FVC ratio ≥0.70, respectively.
Study Design	Double-blinded, placebo-controlled, parallel-group
Primary Endpoint(s)	• Proportion of individuals who experience a 4 unit improvement in SGRQ at 12 weeks and do not meet criteria for treatment failure during the 12 week treatment period.
Secondary Endpoint(s)	• Proportion of individuals with a 2 unit improvement in CAT without treatment failure • Proportion of individuals with a 1 unit improvement in the BDI/TDI without treatment failure • Proportion of individuals with both a 4 unit improvement in SGRQ and a 1 unit improvement in BDI/TDI without treatment failure • Mean change in SGRQ • Mean change in CAT • Mean change in BDI/TDI • $AUC_{0\text{-}3h}$ for FEV_1 • Change from baseline in 12 hour trough FEV_1 (absolute value and % predicted) • Change from baseline in 12 hour trough inspiratory capacity, FEF25-75% and iso-volume FEF25-75% (absolute value and % predicted) • Mean change in symptoms and rescue medication use based on daily diary • Treatment failure defined by increase in lower respiratory symptoms necessitating treatment with active, long-acting inhaled bronchodilator, corticosteroids or antibiotics

Accrual Objective	580 subjects
Study Duration	36 months
Treatment Description	Indacaterol/glycopyrrolate 27.5/15.6 mcg inhaled twice daily vs. placebo
Inclusion Criteria	1. Subject must be able to understand and provide informed consent 2. Age 40-80 3. ≥10 pack-year smoking history 4. Post-bronchodilator FEV_1/FVC ratio ≥0.70 5. Baseline CAT≥10
Exclusion Criteria	1. Inability or unwillingness of a participant to give written informed consent or comply with study protocol. 2. Subject is pregnant, breast-feeding, or plans to become pregnant. 3. Active pulmonary infection or prior pulmonary infection where antibiotic and/or steroid treatment was completed ≤4 weeks prior to enrollment. 4. Post-BD FVC < 70% predicted 5. A primary diagnosis of asthma established by each study investigator based on ATS/ERS criteria as previously implemented in the MACRO clinical trial (1). 6. Known concomitant lung disease, pulmonary tuberculosis (unless confirmed by chest x-ray to be no longer active), or clinically significant bronchiectasis. 7. History (or family history) of long QT syndrome. 8. History of paroxysmal (intermittent) atrial fibrillation will be considered an exclusion. Patients with persistent atrial fibrillation as defined by continuous atrial fibrillation for at least 6 months and controlled with a rate control strategy (i.e., selective beta blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy) for at least 6 months may be considered for inclusion. In such patients, heart rate at enrollment must be < 100/min. 9. Patients with BMI < 15 or more than 40 kg/m2. 10. Patients with diabetes Type I or uncontrolled diabetes Type II. 11. Patients who, in the judgment of the investigator, have a clinically relevant laboratory abnormality or a clinically significant condition such as (but not limited to) significant

	renal disease, psychiatric disease, gastrointestinal disease, unstable ischemic heart disease, arrhythmia (excluding chronic stable atrial fibrillation), uncontrolled hypertension or any other condition which in the opinion of investigator might compromise patient safety or compliance, interfere with evaluation, or preclude completion of the study. 12. Patients with any history of lung cancer. 13. Patients with narrow-angle glaucoma, symptomatic benign prostatic hyperplasia or bladder-neck obstruction or severe renal impairment or urinary retention. Benign Prostatic Hyperplasia (BPH) patients who are stable on treatment can be considered. 14. Any other past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study. 15. Patients with a history of hypersensitivity to any of the study drugs or to drugs from similar chemical classification, including untoward reactions to sympathomimetic amines or inhaled medication or any component thereof. 16. Patients unable to successfully use a dry powder inhaler device or perform spirometry measurements. 17. Use of other investigational drugs at the time of enrollment or within 30 days or 5 half-lives of enrollment, whichever is longer. 18. Patients receiving any prohibited medications in the classes or groups listed in Table 4.3-1. 19. Patients receiving any prohibited COPD related medications in the classes or groups in Table 4.3-2 must undergo the required washout period prior to Visit 1.
Statistical Considerations	Sample size should provide at least 90% power to detect a difference in proportion of subjects who have a 4 unit improvement in SGRQ without treatment failure at 12 weeks in treatment versus placebo arms.

Table of Contents

Glossary of Abbreviations

BD	Bronchodilator
BDI	Baseline Dyspnea Index
CAT	COPD Assessment Test
CFR	Code of Federal Regulations
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DCC	Data Coordinating Center
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
IC	Inspiratory Capacity
ICH	International Conference on Harmonization
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
LABA	Long Acting Beta Agonist
LAMA	Long Acting Muscarinic Antagonist
MCID	Minimum Clinically Important Difference
MI	Myocardial Infarction
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
OHRP	Office for Human Research Protections
PI	[Site] Principal Investigator
RCT	Randomized Controlled Trial
RETHINC	Redefining Therapy in Early COPD
SABA	Short Acting Beta Agonist
SAE	Serious Adverse Event
SAMA	Short Acting Muscarinic Antagonist
SAR	Suspected Adverse Reaction

SGRQ	St. George's Respiratory Questionnaire
SPIROMICS	Subpopulations and Intermediate Outcome Measures in COPD Study
SUSAR	Serious Unexpected Suspected Adverse Reaction
TDI	Transition Dyspnea Index
UP	Unanticipated Problem

1. Background and Rationale

1.1 Critical Knowledge pertinent to the lung disease and intervention

Currently, COPD is defined by having an $FEV_1/FVC<0.7$. In 2011, the GOLD guidelines were revised, recognizing that spirometric staging alone poorly captures disease severity (2). Instead, patients with COPD were divided into four GOLD groups (A-D) based on symptom scores (using standardized questionnaires such as the CAT) and exacerbation risk. Groups A and B correspond to low exacerbation risk, with few symptoms (CAT<10 or mMRC<2) and more symptoms (CAT≥10 or mMRC≥2), respectively. Groups C and D correspond to high risk (GOLD stages 3/4, and/or ≥2 exacerbations annually) with few symptoms (GOLD C) or more symptoms (GOLD D). The first choice for therapy in group B is LABA or LAMA. However, mounting evidence suggests that the spirometric definition of COPD may be insufficient to diagnose COPD at all. Indeed, accumulating data suggest that many current and former smokers with a "normal" FEV_1/FVC (≥0.7), manifest symptoms of COPD, disability due to those symptoms and clinically significant exacerbations (3-5). When carefully studied this group has evidence of occult airflow obstruction consistent with airway disease not detected by simple spirometry. These data suggest that many smokers with symptoms despite normal FEV_1/FVC have chronic obstructive lung disease consistent with COPD, but do not fit current management guidelines. Because this population is large, the health burden posed by those with undiagnosed chronic lung disease is significant (3). Importantly, whether they would benefit from therapy is entirely unknown. A minority of them are already being treated in the community, but without guidance or evidence. **The trial proposed here will test the following overarching hypothesis: current and former smokers with respiratory symptoms despite normal spirometry ($FEV_1/FVC≥0.7$) will derive benefit from inhaled bronchodilator therapy, even though they are excluded from the current GOLD guideline recommendations.** The clinical trial that stems from this hypothesis will provide new fundamental clinical and therapeutic knowledge regardless of the outcome. If these people do benefit from symptom-stratified bronchodilator therapy, then current guidelines for the management of COPD may require significant reconsideration. Such a result would call into question our very definition of COPD, suggesting that our current definition is insufficient to guide basic therapy in a large segment of our population. If these smokers with symptoms despite normal spirometry do not benefit from symptom-stratified bronchodilator therapy, then this result too will provide important guidance for community physicians, given that many patients in this group are already being treated.

1.2 Rationale for Selection of Investigational Agent

The GOLD consensus report (2) and COPD Foundation guidelines (6) currently recommend the use of long-acting bronchodilators, used either alone or in combination, as treatment for patients with COPD with any severity of lung dysfunction who have symptoms based on CAT≥10 or mMRC≥2. Long-acting bronchodilators including the long-acting beta-agonists (indacaterol, formoterol and salmeterol) as well as several long-acting muscarinic antagonists (tiotropium, umeclidinium, and aclidinium) which are all currently FDA approved in the US as monotherapy for the treatment of COPD). The FDA has also approved the use of dual bronchodilators which combine a long-acting beta-agonist (LABA) and a long-acting muscarinic antagonist (LAMA) for maintenance therapy in COPD. These include Anoro™ (umeclidinium/vilanterol) and Stiolto™ (tiotropium/olodaterol). Indacaterol/glycopyrrolate is the dualbronchodilator that we propose to test in our proposal, and it was recently FDAapproved. Indacaterol/glycopyrrolate has rapid onset of action with sustained bronchodilator effect over a 12-hour period and is administered twice daily. Its indication is the long-term maintenance treatment of COPD including chronic bronchitis and/or emphysema.

In clinical studies, both LABAs and LAMAs appear to be effective for improving lung function in terms of FEV_1 although the effects of combination LABA and LAMA are greater than the effects of either drug alone. In the Flight1 and Flight2 studies comparing indacaterol/glycopyrrolate 27.5/15.6 mcg twice daily to indacaterol 27.5 mcg twice daily, glycopyrrolate 15.6 mcg twice daily or placebo, the improvement in FEV_1 area under the curve from 0 to 12 hours (AUC0-12h) for the combination was superior to either monocomponent ($p<0.001$). In addition, symptom improvement based on SGRQ and TDI scores as well as rescue medication use were also significantly greater in the combination treatment group as compared both to monocomponents and placebo ($p<0.001$).

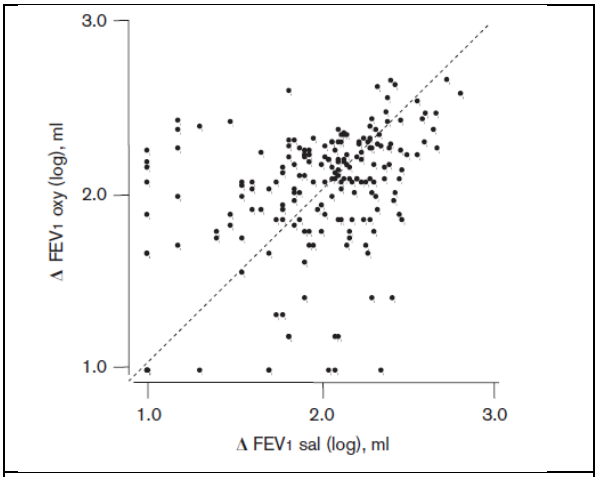


Figure 1 Intraindividual association between β2-adrenergic response on the x-axis (salmeterol) and antimuscarinic response on the y-axis (oxytropium) demonstrating while there is a correlation, significant intra-individual variation exists in FEV_1 improvement with beta-agonist versus antimuscarinic bronchodilators.

In addition to the benefit that dual bronchodilators improve FEV_1 and symptoms more than the monocomponents, there is another advantage to the use of dual bronchodilators in the COPD patient population. While a correlation between bronchodilator responsiveness to a beta-agonist and antimuscarinic in individual patients is observed, there are clearly individuals who respond preferentially to one of the two classes of bronchodilators (**Figure 1**). This preferential response to beta-agonists or antimuscarinics may have a biological underpinning, as differential responses have been associated with polymorphisms in the β2-adrenergic receptor gene (ADRB2) (7).

Hence in choosing a bronchodilator to test in this study, we chose a bronchodilator therapy with dual mechanism of action which is most likely to produce the greatest bronchodilation and symptom improvement in the most number of individuals, allowing us to best test the hypothesis that bronchodilation in symptomatic smokers will result in respiratory symptom improvement. By using maximal bronchodilator therapy we have the best chance of proving or disproving our hypothesis.

1.3 Prior Clinical Studies

The core clinical development program for indacaterol/glycopyrrolate (tradename Utibron) is comprised of: 1) the recently-published Flight 1 and Flight 2 studies which were two, placebo-controlled, parallel group, 12-week randomized studies to characterize the safety and efficacy of indacaterol/glycopyrrolate and 2) Flight 3, a 52-week placebo-controlled study aimed primarily at establishing long-term safety of indacaterol/glycopyrrolate (8, 9). Study populations were male or female greater than 40 years of age with post-bronchodilator FEV_1/FVC<80% predicted, FEV_1 ranging from 30-80% and a minimum of 10 pack-year smoking history. Patients were excluded if they had a history of asthma, prolonged QTc interval or history of respiratory infection in the past 6 weeks prior to screening. The primary endpoint for Flight 1 and 2 was FEV_1 between 0 to 12 h (FEV_1 $AUC_{0\text{-}12h}$) after 12 weeks of treatment with indacaterol/glycopyrrolate as compared to the monocomponents indacaterol and glycopyrrolate. Secondary endpoints included change in percentage of SGRQ responders (defined as individuals experiencing a 4 point drop in SGRQ) in addition to demonstrating superiority of indacaterol/glycopyrrolate compared to placebo in terms of FEV_1 $AUC_{0\text{-}12h}$, the transition dyspnea index (TDI) score, daily rescue medication use and daily symptoms as reported by an e-diary at week 12. 12 week change in quality of life as assessed by the COPD Assessment Test (CAT) was an exploratory endpoint. Pooled data from Flight 1 and 2 demonstrated statistically significant improvement in FEV_1 $AUC_{0\text{-}12h}$ when compared to its respective mono-components in the pooled analysis (treatment difference [Δ] =103 mL and 88 mL versus indacaterol and glycopyrrolate, respectively, p<0.001). In addition, indacaterol/glycopyrrolate treatment was significantly superior to placebo for FEV_1 $AUC_{0\text{-}12h}$ (Δ =246 mL, p<0.001).

Patients treated with indacaterol/glycopyrrolate also had statistically and clinically significant improvement in their SGRQ total score at Week 12 when compared with placebo (mean 5.0 unit improvement, p<0.001).The SGRQ total score also showed a significant reduction with indacaterol/glycopyrrolate treatment compared with indacaterol (p=0.019) and glycopyrrolate (p=0.033). A significantly higher proportion of patients (responders) in the indacaterol/glycopyrrolate group also achieved the minimum clinically important difference (MCID) of 4 units when compared to placebo (odds ratio of 2.5, p<0.001), indacaterol (odds ratio of 1.3, p=0.041) and glycopyrrolate (odds ratio of 1.5, p=0.003). Importantly, the the indacaterol/glycopyrrolate treatment arm also had a statistically and clinically significant improvement (defined as ≥1 unit increase) in the TDI total score compared with placebo (1.64 unit improvement, p<0.001), and statistical improvements as compared to

indacaterol (0.78 unit improvement, p<0.001) and glycopyrrolate (0.73 unit improvement, p<0.001) at Week 12. The proportion of patients with a MCID ≥1unit in the TDI total score was significantly higher with indacaterol/glycopyrrolate compared with placebo, indacaterol and glycopyrrolate. For TDI, the odds ratio for responder rate (with response defined by 1 unit change from baseline) at 12 weeks was 1.58 (95% CI 0.97, 2.57) and 2.19 (95% CI 1.33, 3.60). For SGRQ, the odds ratio for responder rate (with response defined by a 4 unit change from baseline) was 1.71 (95% CI 1.05, 2.78) and 1.80 (95% CI 1.08, 2.98). There was also a significant reduction in mean daily puffs and increase in percentage of days with no rescue medication use with indacaterol/glycopyrrolate compared with placebo. An exploratory endpoint in the Flight studies was the change in health-related quality of life assessed by COPD Assessment Test (CAT) at Week 12. Using pooled data, a mean difference of 1.8 (95% CI 1.1, 2.4) units CAT score improvement was seen in the indacaterol/glycopyrrolate group as compared to placebo (p<0.001). The difference between indacaterol/glycopyrrolate and monocomponents was also statistically significant at the p<0.05 level.

1.4 Rationale for Study Population

For simplicity we will refer to current and former smokers with $FEV_1/FVC \geq 0.7$ as GOLD 0 subjects. Our preliminary data from the NHLBI-funded SPIROMICS study suggest that a significant percentage of GOLD 0 subjects have symptoms, exacerbations, activity limitation and airway wall thickening consistent with airway disease not detected by simple spirometry. The SPIROMICS study is an ongoing longitudinal observational study of current and former smokers (≥ 20 pack years) with a range of airflow obstruction and never-smoking controls. In preliminary data we categorized GOLD 0 smokers and subjects with GOLD I/II COPD as symptomatic (CAT≥10) or asymptomatic (CAT<10). We used CAT because we have previously shown that the mMRC≥2 and CAT≥10 (both used by GOLD for identifying symptomatic patients in GOLD I-IV) are not equivalent and that the mMRC≥2 is overly stringent (10). We also provide corroborating evidence where available from another NHLBI study, COPDGene. While CAT was not collected in COPDGene, we use SGRQ≥25 which is approximately equivalent to CAT≥10 (11).

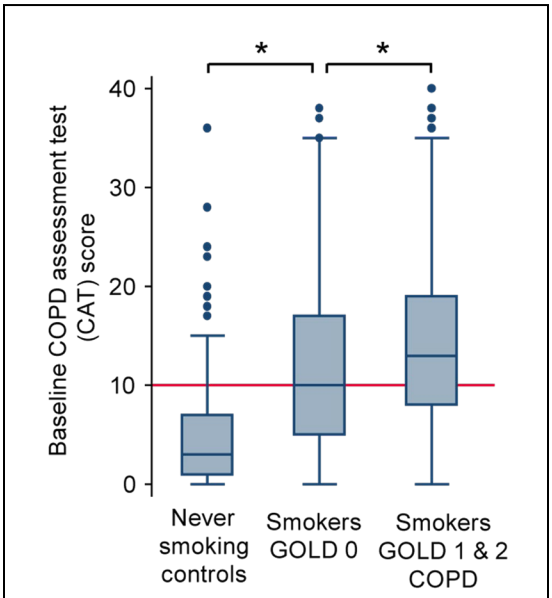


Figure 1. In SPIROMICS, 52% of GOLD 0 smokers have elevated symptoms of COPD (defined as CAT≥10.

Many GOLD 0 current and former smokers have clinically important symptoms of COPD. In SPIROMICS we found that 52% of GOLD 0 subjects had CAT≥10 (Figure 1), slightly less than the prevalence of CAT≥10 in GOLD 1&2 (65%, p<0.001) but far greater than the prevalence in never-smoking controls (16%, p<0.001).

Symptomatic GOLD 0 smokers had higher prospective rates of exacerbation of respiratory disease and shorter 6 minute walk distance (6MWD). In SPIROMICS, whether defined based on use of antibiotics, systemic corticosteroids, both medications, any health care utilization, or hospitalization/emergency department (ED) visits (severe exacerbations), the prospective rate of exacerbations was higher in GOLD 0 smokers with CAT≥10 than in GOLD 0 with CAT<10 or healthy never-smoking controls (Figure 2). The 6MWD was also lower in GOLD 0 with CAT≥10 (408±100m) as compared to both GOLD 0 with CAT<10 (462±92m) and GOLD 1&2 subjects with CAT<10 (452±101m) (all p<0.05).

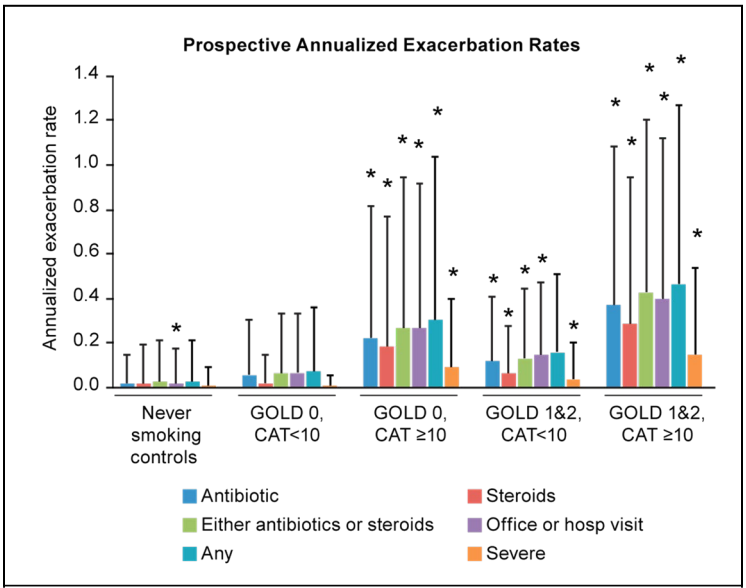


Figure 2. Increased symptoms (CAT≥10) are associated with increased prospective rates of exacerbations in GOLD 0 subjects.

In COPDGene, walk distance was similarly reduced in symptomatic subjects with normal spirometry vs. asymptomatic subjects (402±104m vs 471±102m, p<0.001).

Symptomatic GOLD 0 current/former smokers have decreased inspiratory capacity, consistent with occult airflow obstruction. In SPIROMICS, we found that the post-bronchodilator inspiratory capacity (IC) was 2.66±0.74 in symptomatic GOLD 0 subjects vs 2.88±0.75 in asymptomatic GOLD 0 subjects, p=0.001). The IC in this group was similar to symptomatic GOLD I/II patients (2.67±0.81, p=0.48) and worse than asymptomatic GOLD I/II patients (2.88±0.84, p=0.004). This decreased IC is not explained by emphysema as the percent of lung <-950 Hounsfield units (HU) by quantitative chest HRCT in symptomatic GOLD 0 subjects was low and no different from asymptomatic subjects (p=0.99). Instead, symptomatic GOLD 0 subjects have a higher Pi10 (a measure of airway wall thickness) than asymptomatic GOLD 0 subjects (3.73±0.090 vs 3.70±0.090, p<0.05). Hence we hypothesize that these physiologic changes are due to occult airway disease. While we could find no studies of bronchodilators in GOLD 0 subjects, several studies in GOLD I patients demonstrate the benefit of bronchodilators in terms of improvements in inspiratory capacity, functional residual capacity, residual volume, airways resistance, dynamic hyperinflation and work of breathing (12-15).

Many symptomatic GOLD 0 current/former smokers are already being treated for COPD, with great variability in medication choice. In SPIROMICS, 43% of these subjects were on bronchodilators: 31% SABA and 11% SAMA; 31% LAMA and 15% LABA. Finally, 23% were using inhaled corticosteroids.

In the above analyses, all spirometry was post-bronchodilator and all p-values were Bonferroni-corrected for multiple comparisons across four groups (symptomatic/GOLD 0, asymptomatic GOLD 0, symptomatic/GOLD I&II, and asymptomatic GOLD I&II). Current smoking was more common in symptomatic as compared to asymptomatic GOLD 0 subjects (58% vs. 42%, p<0.001), and the BMI was higher (29.8±5.4 vs 27.8±4.7, p<0.001). Therefore all of the above analyses were repeated while controlling for current smoking, BMI as well as age, gender, race, ethnicity, congestive heart failure, GERD self-report, and any asthma diagnosis, and there was no material change in the results in these adjusted models.

Summary of our rationale for the study population: We show that respiratory symptoms are common in GOLD 0 current/former smokers (i.e. with $FEV_1/FVC \geq 0.7$ post-bronchodilator), and that GOLD 0 smokers with symptoms have higher rates of respiratory exacerbation, activity limitations, and evidence of occult airflow obstruction (decreased inspiratory capacity). Our data also indicate that this is not due to emphysema but is instead associated with airway wall thickening, and we hypothesize that this occult airway disease will respond to effective bronchodilator therapy.

1.5 Feasibility of the Intervention in the Target Population

Indacaterol/glycopyrrolate 27.5/15.6 mcg inhaled twice daily is simple to use and should be feasible in terms of ease of use and tolerability in the target population for this study (symptomatic smokers with $FEV_1/FVC \geq 0.70$) as it is in the population for which it was developed (symptomatic smokers with $FEV_1/FVC < 0.70$). While an RCT of long-acting bronchodilator therapy in symptomatic GOLD 0 smokers (i.e. those with $FEV_1/FVC \geq 0.70$)

has never been performed, several studies in GOLD I patients demonstrate the benefit of bronchodilators in terms of improvements in inspiratory capacity, functional residual capacity, residual volume, airways resistance, dynamic hyperinflation and work of breathing (12-15). As outlined above in 1.2., there is also evidence that the degree of FEV_1 improvement and symptom improvement defined by percentage of subjects with 4 point drop in SGRQ with indacaterol/glycopyrrolate therapy actually increases in parallel with FEV_1. In summary these data provide rationale for long-acting bronchodilator therapy in the target population for this proposal.

2. Study Hypotheses/Objectives

2.1 Hypotheses

The study proposed here will test the hypothesis that symptomatic current and former smokers with spirometric values within the normal range (post-bronchodilator $FEV_1/FVC \geq 0.70$ and post-BD FVC ≥ 70% predicted [to guard against restrictive lung disease]) will still derive symptomatic benefit from long-acting bronchodilator therapy even though they are excluded from current GOLD guideline recommendations.

2.2 Primary Objective

Proportion of individuals who experience a 4 unit improvement in SGRQ and do not meet criteria for treatment failure during the 12 week study period.

2.3 Secondary Objectives

- Proportion of individuals with 2 unit improvement in CAT without treatment failure
- Proportion of individuals with a 1 unit improvement in BDI/TDI without treatment failure
- Proportion of individuals with both a 4 unit improvement in SGRQ and a 1 unit improvement in BDI/TDI without treatment failure
- Mean change in SGRQ
- Mean change in CAT
- $AUC_{0\text{-}3h}$ for FEV_1
- Change from baseline in trough FEV_1 (absolute value and % predicted)
- Change in baseline from trough inspiratory capacity, FEF25-75% and iso-volume FEF25-75% (absolute value and % predicted)
- Mean change in level of symptoms and rescue medication use based on daily diary
- Treatment failure defined by increase in lower respiratory symptoms necessitating treatment with active, long-acting inhaled bronchodilator, corticosteroids or antibiotics.

2.4 Anticipated Short and Long Term Impact of the Intervention

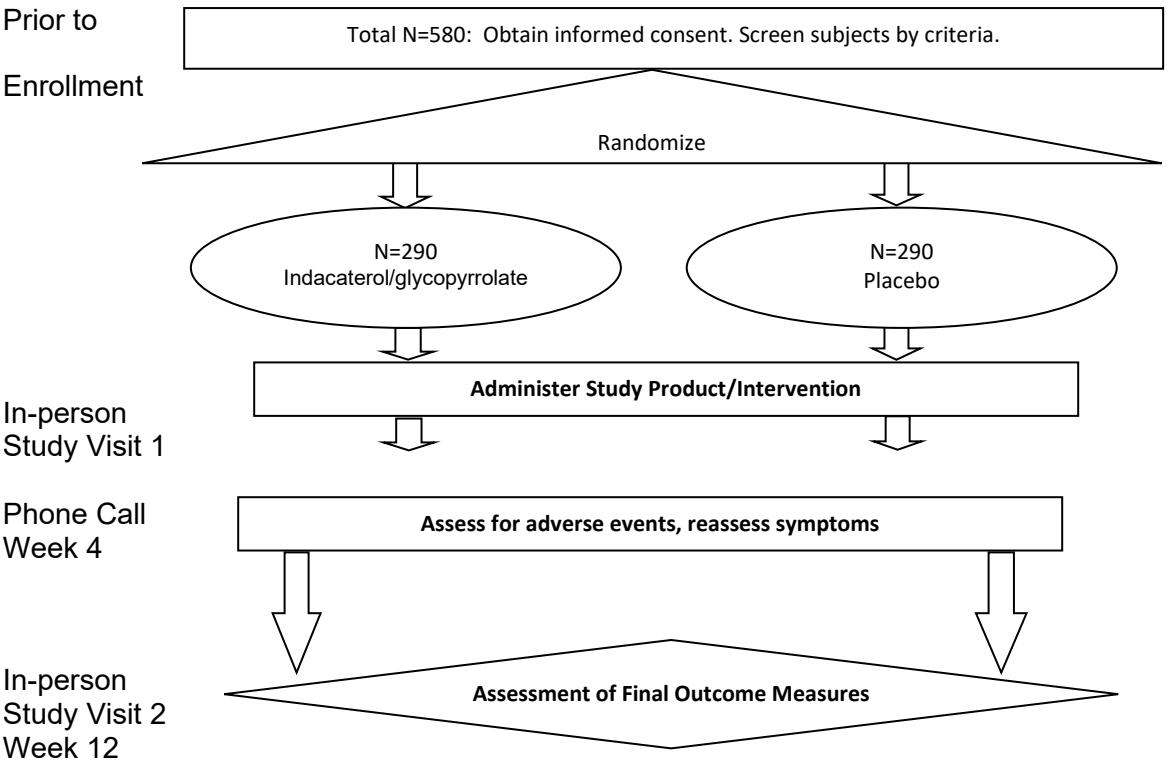
As this is a 12-week interventional trial, we expect the short term impacts of the intervention to be evidenced by improvement in the primary outcome measure, specifically improvements in symptoms as measured by proportion of individuals experiencing a 4 unit improvement in SGRQ and do not meet criteria for treatment failure during the 12 week study period. We hope that the long term impacts of this study will be to further investigation in this population of patients and to influence both how we as a research and medical community define and treat COPD. While this is not a study of smoking cessation, we will be including current and former smokers and as such realize this is an opportunity to provide medical information on respiratory health effects of smoking. As part of the study, information on smoking cessation resources will be provided to all currently smoking participants at the time of first in-person contact.

3 Study Design

3.1 Description of Study Design

RETHINC is a Phase III, double-blind, placebo-controlled, parallel-design multi-site study comparing indacaterol/glycopyrrolate 27.5/15.6 mcg inhaled twice daily vs placebo in subjects with ≥10 pack-years smoking history with post-bronchodilator $FEV_1/FVC \geq 0.70$ and CAT ≥ 10. Treatment duration is 12 weeks with 290 patients in each arm. SGRQ, CAT, BDI/TDI and spirometry will be performed at baseline and 12 weeks. A phone call at 4 weeks will assess for adverse events.

Figure 3.1-1. Flow Diagram



3.2 Primary Endpoint(s)/Outcome(s)

The primary study endpoint will be comparison of the proportion of individuals on treatment versus placebo who experience a 4 unit change in SGRQ after 12 weeks and do not meet criteria for treatment failure during the 12 week study period. If we meet our primary outcome we will conclude that treatment improves clinical status in symptomatic "at risk" smokers even if they do not meet the formal spirometric definition of COPD ($FEV_1/FVC<0.7$).

3.3 Secondary Endpoint(s)/Outcome(s)

Important secondary endpoints in comparing treatment versus placebo after 12 weeks will be proportion of individuals with 2 unit change in CAT without treatment failure; proportion of individuals with a 1 unit change in BDI/TDI without treatment failure; proportion of individuals with both a 4 unit improvement in SGRQ and a 1 unit improvement in BDI/TDI without treatment failure; mean change in SGRQ; mean change in CAT; $AUC_{0\text{-}3h}$ in FEV_1; change from baseline in 12 hour trough FEV_1; change from baseline in 12 hour trough inspiratory capacity, FEF25-75% and iso-volume FEF25-75% and mean change symptoms and rescue medication use based on daily diary; and treatment failure defined by increase in lower respiratory symptoms necessitating treatment with active, long-acting inhaled bronchodilator, corticosteroids or antibiotics.

3.4 Survey Instruments to be Used

SGRQ The St. George's Respiratory Questionnaire (SGRQ) is a validated health status instrument developed for COPD that contains 50 items divided into three components: "Symptoms" concerned with respiratory symptoms, their frequency and severity; "Activity" concerned with activities that cause or are limited by breathlessness; and "Impacts" which covers a range of aspects concerned with social functioning and psychological disturbances resulting from airway disease (16). A score will be calculated for each component and a "Total" score will also be calculated. In each case the lowest possible value is zero and the highest 100. Higher values correspond to greater impairment of quality of life. The accepted minimal clinically important difference (MCID) for SGRQ is a 4 unit change (17). At the 12 week visit, subjects will be instructed to provide responses to SGRQ that reflect their health status during the 12 week treatment period.

CAT The COPD Assessment Test is a validated, short and simple patient completed questionnaire which has been developed for use in routine clinical practice to measure the health status of patients with COPD (11, 18). The CAT is an 8-item questionnaire suitable for completion by all patients diagnosed with COPD. When completing the questionnaire, subjects rate their experience on a scale, ranging from 0 (minimum impairment) to 5 (maximum impairment) with a scoring range of 0-40. Higher scores indicate greater disease impact. The accepted MCID for CAT is a 2 unit change (19).

BDI/TDI Dyspnea will be measured at baseline using the baseline dyspnea index (BDI) and during the treatment period using the transition dyspnea index (TDI), which captures changes from baseline. The BDI and TDI were originally developed to assess dyspnea in patients with a variety of respiratory conditions including COPD. Each have three domains; functional impairment, magnitude of task and magnitude of effort. The BDI domains are rated from 0 (severe) to 4 (unimpaired) and the rates are summed for the baseline focal score ranging from 0 to 12; the lower the score the worse the severity of dyspnea. The TDI domains are rated from -3 (major deterioration) to 3 (major improvement) and the rates are summed for the transition focal score ranging from -9 to 9; minus scores indicate deterioration. The accepted MCID for TDI is 1 unit change (20).

3.5 Stratification, Randomization, and Blinding/Masking

A permuted block randomization scheme will be created with varying block sizes stratified by clinical center, smoking history (current smoker/former smoker) and prior maintenance treatment for COPD requiring washout. Once a subject has completed the screening and evaluation for inclusion/exclusion criteria, the randomization process will begin. Subjects will be randomized to receive active drug and placebo with equal probability (1:1), via Internet with a central interactive response system (IVRS). On the day of randomization, after the subject has successfully met all inclusion and exclusion criteria, the investigator or designee will login to the central randomization website to obtain the assigned kit randomization number for that subject. One pharmacist at each site will be unblinded to treatment group. For resupply of the site, the pharmacy will need to notify the NEMO to request the next shipment of drug supply when on-site drug supply is down to one placebo kit or one active drug kit. The trial results will be reported according to guidelines specified in the CONSORT statement. A flow diagram describing screening, recruitment, randomization, dropout, and vital status will be included in the primary manuscript. AEs and efficacy data will be presented by the 2 treatment groups. Adherence, dropout, and loss to follow-up will be carefully examined across the 2 treatment groups. Analyses of safety will be based on data from all randomized subjects who received at least 1 dose of study drug.

3.5.1 Procedure for Unblinding/Unmasking

Unblinding must be approved by the DSMB unless an immediate life threatening condition has developed and the Protocol Chairs are not accessible. In the case of emergent unblinding, the site investigator will notify the protocol chairs and the DCC of the unblinding event on the next business day; the protocol chairs and the DCC

will then notify the DSMB and FDA. A full account of the event will be recorded, including the date and time of the unblinding, the reason for the decision to unblind, and the name of the individual who made the decision and the roles of who was notified and unblinded (i.e. coordinator, PI, subject, etc). The reasons for unblinding of a participant's treatment will be included in the final study report.

3.5.2 Securing Blinding and Randomization Information

All subjects, monitors, and study center personnel related to the study, except for the pharmacist (or qualified designee) who prepares the study drug and the pharmacy monitor who monitors the pharmacy records and procedures, will be blinded to study treatment throughout the study. A designated statistician will securely maintain an unblinded randomization schema.

4 Selection of Participants and Clinical Sites/Laboratories

4.1 Inclusion Criteria

Individuals who meet all of the following criteria are eligible for enrollment as study participants:

1. Subject must be able to understand and provide informed consent
2. Age 40-80
3. ≥10 pack-year smoking history
4. Post-bronchodilator FEV_1/FVC ratio ≥0.70
5. Baseline CAT≥10

4.2 Exclusion Criteria

Individuals who meet any of these criteria are not eligible for enrollment as study participants:

1. Inability or unwillingness of a participant to give written informed consent or comply with study protocol.
2. Subject is pregnant, breast-feeding, or plans to become pregnant.
3. Active pulmonary infection or prior pulmonary infection where treatment was completed ≤ 4 weeks prior to enrollment.
4. Post-BD FVC < 70% predicted.
5. A primary diagnosis of asthma established by each study investigator on the basis of the American Thoracic Society/European Respiratory Society guidelines as implemented in the MACRO study (1).

   In this implementation, physician investigators are asked apply the criteria above and if, after applying the these criteria, the clinicians are still unsure about the distinction in a specific patient, then bronchodilator testing with inhaled albuterol will be performed and patients with changes in FEV_1 > 400 mL will be excluded.

Clinical Features Differentiating COPD and Asthma

History	COPD	Asthma
Smoker or ex-smoker	Nearly all	Possibly
Symptom onset < 35 yrs	Rare	Common
Chronic productive cough	Common	Uncommon
Breathlessness	Persistent and progressive	Variable
Nighttime waking with breathlessness and wheeze	Uncommon	Common
Significant diurnal or day-to-day variation of symptoms	Uncommon	Common

6. Known concomitant lung disease, pulmonary tuberculosis (unless confirmed by chest x-ray to be no longer active), or clinically significant bronchiectasis.
7. History (or family history) of long QT syndrome.
8. History of paroxysmal (intermittent) atrial fibrillation will be considered an exclusion. Patients with persistent atrial fibrillation as defined by continuous atrial fibrillation for at least 6 months and controlled with a rate control strategy (i.e., selective beta blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy) for at least 6 months may be considered for inclusion. In such patients, heart rate at enrollment must be < 100/min.
9. Patients with BMI < 15 or more than 40 kg/m2.
10. Patients with diabetes Type I or uncontrolled diabetes Type II.
11. Patients who, in the judgment of the investigator, have a clinically relevant laboratory abnormality or a clinically significant condition such as (but not limited to) significant renal disease, psychiatric disease, gastrointestinal disease, unstable ischemic heart disease, arrhythmia (excluding chronic stable atrial fibrillation), uncontrolled hypertension or any other condition which in the opinion of investigator might compromise patient safety or compliance, interfere with evaluation, or preclude completion of the study.
12. Patients with any history of lung cancer.
13. Patients with narrow-angle glaucoma, symptomatic benign prostatic hyperplasia or bladder-neck obstruction or severe renal impairment or urinary retention. Benign Prostatic Hyperplasia (BPH) patients who are stable on treatment can be considered.
14. Any other past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study.
15. Patients with a history of hypersensitivity to any of the study drugs or to drugs from similar chemical classification, including untoward reactions to sympathomimetic amines or inhaled medication or any component thereof.
16. Patients unable to successfully use a dry powder inhaler device or perform spirometry measurements.
17. Use of other investigational drugs at the time of enrollment or within 30 days or 5 half-lives of enrollment, whichever is longer.
18. Patients receiving any prohibited medications in the classes or groups listed in Table 4.3-1.
19. Patients receiving any prohibited COPD related medications in the classes or groups in Table 4.3-2 must undergo the required washout period prior to Visit 1.

The class of medications listed in Table 4.3-1 are not permitted to be taken during the study and are considered exclusion criteria. Medications in Table 4.3-2 are also not permitted but subjects may be washed out per protocol, see Section 7. If a patient requires any of these medications and they cannot be safely washed out (with permission of the subject's primary physician) then they should not be included in the study. Short acting beta agonists are the only "rescue" medication allowed during the trial. Each concomitant drug must be individually assessed against all exclusion criteria and the tables below to see if it allowed. If in doubt you should contact the Protocol Chairs before randomizing a patient or allowing a new medication to be started.

4.3 Prohibited Medication

Table 4.3-1 Prohibited Medications

Class of medication
Cardiac anti-arrhythmics Class Ia
Cardiac anti-arrhythmics Class III
Tricyclic antidepressants
Monoamino-oxidase inhibitors

Other investigational drugs

NOTE: If participant is on a non-potassium sparing diuretic (unless administered as a fixed-dose combination, i.e. all in one pill/tablet with a potassium conserving drug or has adequate documentation of concomitant use of a potassium conserving drug), we require them to have a serum potassium level check either at the enrollment visit or at a separate screening visit and to exclude them if they have a potassium level that is below the lower limit of normal for that laboratory. The serum potassium level must be available and reviewed before randomization. If it is desired that a patient initiate a non-potassium sparing diuretic (not as part of fixed-dose combination) after the subject has been randomized, a potassium level that is above the lower limit of normal for the chosen laboratory should be documented if on study drug.

Table 4.3-2 Prohibited COPD-related Medications Requiring Washout Period of 30 days

Class of medication	Minimum washout period prior to Visit 1
Long-acting anticholinergics	30 days
Short-acting anticholinergics	30 days
Fixed combinations of long-acting beta-agonists and inhaled corticosteroids	30 days
Fixed combinations of short acting beta agonists and short-acting anticholinergics	30 days
Long-acting beta agonists	30 days

4.4 Recruitment and Retention

A variety of recruitment techniques at each center should be employed as allowed by local IRB's including local advertising aimed at (a) health system patients; (b) smoking cessation groups; (c) general public, including social media; (d) review of local databases or patient registries; (e) pulmonary function test database and electronic medical record query; (f) screening of pulmonary clinics, (g) lung cancer screening clinics and (h) primary care clinics. The study will also be posted on clinicaltrials.gov. Due to the short duration of the study and low number of study visits, we expect attrition to be low. However, we will also work with the clinical centers to keep logistical burden on subjects to a minimum.

4.5 Training of Clinical Centers

At clinical center initiation, the DCC Project Manager will be responsible for training and certification sessions, including training on required software and systems, study procedures and eCRFs for study coordinators, PIs, and other study staff as needed. The site training is a critical study milestone necessary before a site can start enrolling subjects into the study. Due to limited budget, instead of onsite visits, webinars will be used to conduct site training. A Manual of Operations will be written by the DCC Project Manager, describing detailed study procedures that augment the protocol will be posted on the website. It is updated regularly as changes and refinements to the study are taken.

5. Known and Potential Risks and Benefits to Participants

5.1 Risks of Investigational Product or Intervention

Adverse drug reactions

Data provided from the prescribing information (package insert) approved by the FDA for indacaterol/glycopyrrolate is outlined in Table 5.1-1.

Table 5.1-1 Adverse Events with Indacaterol/glycopyrrolate greater than or equal to 1% incidence and higher than placebo in COPD patients

	Indacaterol/glycopyrrolate 27.5/15.6 mcg BID	Indacaterol 27.5 mcg BID	Glycopyrrolate 15.6 mcg BID	Placebo
Nasopharyngitis	21 (4.1%)	13 (2.5%)	12 (2.3%)	9 (1.8%)
Hypertension	10 (2.0%)	5 (1.0%)	3 (0.6%)	7 (1.4%)
Back pain	9 (1.8%)	7 (1.4%)	2 (0.4%)	3 (0.6%)
Oropharyngeal pain	8 (1.6%)	4 (0.8%)	8 (1.6%)	6 (1.2%)

Other adverse reactions occurring more frequently with indacaterol/glycopyrrolate than with placebo, but with an incidence of less than 1% include dyspepsia, gastroenteritis, chest pain, fatigue, peripheral edema, rash/pruritus, insomnia, dizziness, bladder obstruction/urinary retention, atrial fibrillation, palpitations, tachycardia. Additional adverse reactions that were reported in registration trials included upper and lower respiratory tract infection, pneumonia, diarrhea, headache, gastroesophageal reflux disease, hyperglycemia, rhinitis.

In addition, indacaterol/glycopyrrolate can produce paradoxical bronchospasm that may be life-threatening. Immediate hypersensitivity reactions have been reported after administration of indacaterol or glycopyrrolate. Indacaterol, like other beta2-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. Indacaterol/glycopyrrolate also has the potential to worsen pre-existing chronic conditions including urinary retention and narrow-angle glaucoma.

Contraindications

All long acting beta agonists are contraindicated in patients with asthma without the use of long-term asthma controller medications. Per protocol, patients with a primary diagnosis of asthma will be excluded from participation in this study.

5.2 Risks of Other Protocol Specified Medications

Albuterol is an inhaled, short-acting beta-agonist that will be used to perform post-bronchodilator spirometry. Dosage of albuterol administered in these scenarios is 90 mcg per actuation or 360 mcg total. In clinical studies, at least 3% of patients taking albuterol report headache, tachycardia (increased heart rate), muscle pain, dizziness, pharyngitis (sore throat), and rhinitis (runny nose). Less than 3% of patients taking albuterol report chest pain, infection, diarrhea, glossitis (swelling of the tongue), anxiety, dyspnea (difficulty breathing), ear disorder, ear pain, and urinary tract infection. In small cumulative dose studies, tremor, nervousness, and headache were most frequently reported.

5.3 Risks of Study Procedures

Demographic and health status information: Subjects could experience fatigue or frustration during the completion of health status instruments.

Physiologic studies: Mild respiratory distress, transient desaturation, and lightheadedness can be seen during the pulmonary function testing. These are rarely significant if testing is performed by trained personnel such as those involved in this study. Participants will be monitored closely during the procedure.

Washout: For subjects requiring washout of an inhaled respiratory medication, participants could experience increased respiratory distress. If significant symptoms are experienced during the washout period, the subjects will not be enrolled in the study.

Research Lab/Venipuncture: The risk associated with blood draws can include but is not limited to pain, bruising, or superficial phlebitis. The vein in which the needle has been inserted to draw blood may become sore and red. A temporary "black and blue mark" may develop, and rarely fainting may occur.

5.4 Potential Benefits

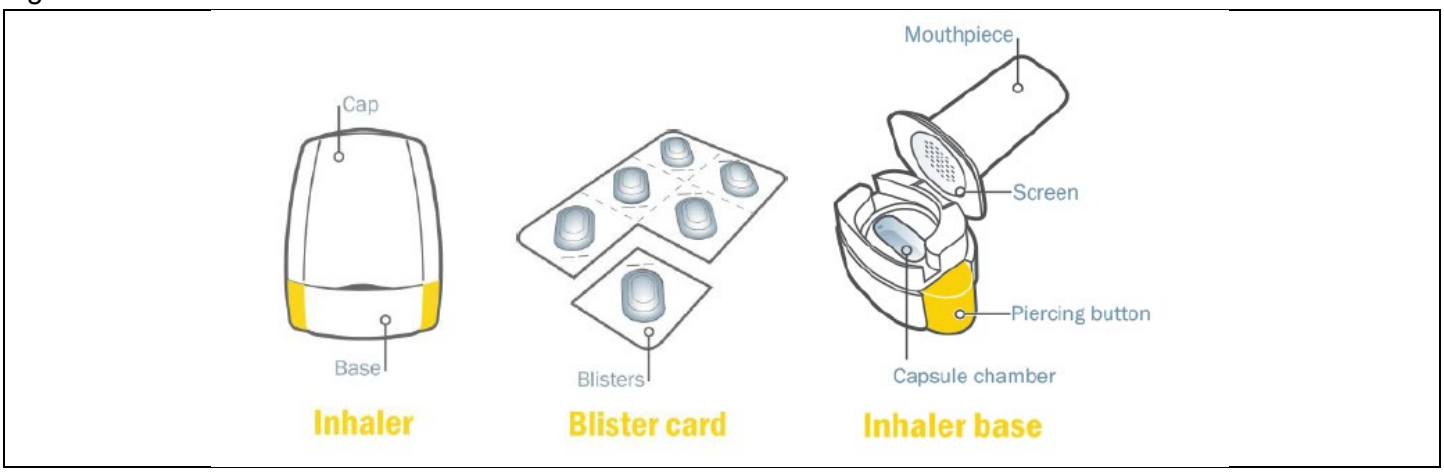
Participating subjects may benefit from the intervention in terms of a reduction in respiratory symptoms including shortness of breath, wheezing and cough. This study may also benefit society in demonstrating treatment efficacy of long acting bronchodilator therapy in patients currently not included in COPD treatment guidelines.

6. Investigational Agent/Device/Intervention

6.1 Investigational Agent/Device

The investigational agent is indacaterol/glycopyrrolate 27.5/15.6 mcg inhaled twice daily. This drug has been extensively studied in COPD and is FDA approved for treatment of COPD in the US. Administration of this medication involves removing capsule from a blister pack, placing the capsule in the Neohaler device, puncturing the capsule with the device and inhaling via the mouthpiece, see Figure 6.1-1.

Figure 6.1-1. Neohaler.



6.2 Drug Accountability

Under Title 21 of the Code of Federal Regulations (21CFR §312.62) the investigator will maintain adequate records of the disposition of the investigational agent, including the date and quantity of the drug received, to whom the drug was dispensed (participant-by-participant accounting), and a detailed accounting of any drug accidentally or deliberately destroyed.

Records for receipt, storage, use, and disposition will be maintained by the study site. A drug-dispensing log will be kept current for each participant. This log will contain the identification of each participant and the date and quantity of drug dispensed.

All records regarding the disposition of the investigational product will be available for inspection. Indacaterol/glycopyrrolate will be dispensed to the sites by the DCC or designee.

6.3 Assessment of Adherence to the Investigational Agent

Compliance will be assessed through indacaterol/glycopyrrolate capsule counts at the final study visit.

7. Study Procedures

7.1 Pre-screening Phone Call All Subjects

Subjects will be evaluated by pre-screening phone call prior to the screening and enrollment visit (Visit 1). During the pre-screening phone call, study staff will review the inclusion and exclusion criteria with the subject to determine their eligibility. This will include administration of the CAT questionnaire by phone to determine whether score meets enrollment criteria of ≥ 10. If subject is eligible a screen/enrollment visit will be scheduled. If subject is ineligible due to factors that may be subject to change over time (e.g. BMI drops or a prohibited medication has been discontinued for clinical reasons), subjects may be undergo phone call re-screening. Even subjects who are brought in for a Visit 1 may be re-screened (see 7.2).

If the subject is currently taking a prohibited COPD medication from Table 4.3-2, the subject may be brought in for an additional on-site screening visit (visit 0) to be consented and the COPD medication discontinued, after seeking agreement from the subject's primary provider. Subjects will be strictly instructed that if they cannot tolerate being off of their COPD medication, then they should restart their COPD medication and notify us. The subject will be called 3 weeks after the COPD medication discontinued to see if they are tolerating washout and if so, be brought back for Visit 1, 30 days after the initial on-site screening visit.

7.2 Screening/Enrollment (non washout subjects, Visit 1)

A subject number will be assigned at this time of signed informed consent. The required order of completion of these assessments will be further outlined in the Manual of Procedures.

- Inclusion/exclusion criteria assessment
- Demographics information including date of birth, sex, race and ethnicity, height, weight
- Relevant medical history including smoking status and history, documented history of respiratory infection treated in the past 30 days with antibiotics or steroids and asthma diagnosis (see exclusion criteria).
- Current concomitant medications (See Note).
- Current and prior COPD medication history used in the 12 months prior to Visit
- Physical Exam and vital signs
- Completion of questionnaires including SGRQ, CAT and BDI
- FEV_1, FVC, SVC and IC before and 15 mins after 4 puffs of albuterol
- Pregnancy test is required for females of child bearing potential prior to randomization.
- Distribution of diary cards and study drug.
- Education on the benefits of smoking cessation and resources for help with smoking cessation

NOTE: If participant is on a non-potassium sparing diuretic (unless administered as a fixed-dose combination, i.e. all in one pill/tablet with a potassium conserving drug, or has adequate documentation of concomitant use

of a potassium conserving drug), we require them to have a serum potassium level check either at the enrollment visit or at a separate screening visit and to exclude them if they have a potassium level that is below the lower limit of normal for that laboratory. The serum potassium level must be available and reviewed before randomization. If the level is checked and is above the lower limit of normal for the chosen laboratory, the subject may be enrolled into the study. If it is desired that a patient initiate a non-potassium sparing diuretic (not as part of fixed-dose combination) after the subject has been randomized, a potassium level that is above the lower limit of normal for the chosen laboratory should be documented if on study drug.

Subjects who meet enrollment criteria will be randomized to indacaterol/glycopyrrolate versus placebo at this visit. If at this visit the subject is determined to be taking a prohibited COPD medication from Table 4.3-2, the patient may still be enrolled after a 30 day wash-out at which point the subject would be brought back for a Visit 1 (follow Schedule of Events for Washout Subjects). At this visit, every patient will be encouraged to increase physical activity during the study period.

Subjects who do not meet enrollment criteria at Visit 1 may be brought back to repeat Visit 1 for potential enrollment. Rationale to rescreen includes factors that may be subject to change over time (e.g. BMI drops or a prohibited medication has been discontinued for clinical reasons). In such cases, all Visit 1 procedures will be repeated.

7.3 Washout visit (washout subjects only, Visit 0)

Subjects taking medications in Table 4.3-2 will require medication washout prior to enrollment. For these subjects, see 7.9 for schedule of events for participants requiring wash-out. For these subjects, an additional on-site washout visit will be performed. Note during this visit a shortened, post-bronchodilator only spirometry will be performed. The subsequent medication washout period is 30 days. A phone call performed one week prior to enrollment (Visit 1) will be performed to determine if subject tolerated the wash-out. Subjects who tolerate wash-out may proceed to enrollment. See 7.9 for schedule of events for the enrollment visit for washout subjects.

Assessments conducted during this visit will include:

- Inclusion/exclusion criteria assessment
- Demographics information including date of birth, sex, race and ethnicity, height, weight
- Relevant medical history including smoking status and history, documented history of respiratory infection treated in the past 30 days with antibiotics or steroids and asthma diagnosis (see exclusion criteria).
- Current concomitant medications (See Note).
- Current and prior COPD medication history used in the 12 months prior to Visit
- Physical Exam and vital signs
- Completion of CAT
- FEV_1 and FVC 15 mins after 4 puffs of albuterol

7.4 Phone Call (washout subjects only, Week 3)

- Current concomitant medications (See Note).
- Interim medical history including need for antibiotics and/or steroids for a respiratory event including review of smoking status.

7.5 Screening/Enrollment (washout subjects only, Visit 1)

Assessments conducted during this visit will include:

- inclusion/exclusion criteria assessment
- FEV_1, FVC, SVC and IC before and 15 mins after 4 puffs of albuterol
- Pregnancy test is required for females of child bearing potential prior to randomization.
- Distribution of diary cards and study drug.
- Interim medical history including need for antibiotics and/or steroids for a respiratory event including review of smoking status.
- Physical Exam and vital signs
- Completion of questionnaires including SGRQ, CAT and BDI
- Review of concomitant medications (See Note).

NOTE: If participant is on a non-potassium sparing diuretic (unless administered as a fixed-dose combination, i.e. all in one pill/tablet with a potassium conserving drug, or has adequate documentation of concomitant use of a potassium conserving drug), we require them to have a serum potassium level check either at the enrollment visit or at a separate screening visit and to exclude them if they have a potassium level that is below the lower limit of normal for that laboratory. The serum potassium level must be available and reviewed before randomization. If the level is checked and is above the lower limit of normal for the chosen laboratory, the subject may be enrolled into the study. If it is desired that a patient initiate a non-potassium sparing diuretic (not as part of fixed-dose combination) after the subject has been randomized, a potassium level that is above the lower limit of normal for the chosen laboratory should be documented if on study drug.

Washout subjects who do not meet enrollment criteria at Visit 1 may be rescreened if their primary care physician allows them to maintain the washout. In such instances, washout subjects would be brought back to repeat Visit 1. Rationale to rescreen includes factors that may be subject to change over time (e.g. BMI drops or a prohibited medication has been discontinued for clinical reasons). In such cases, all Visit 1 procedures will be repeated.

7.6 Phone Call (all subjects, Week 4)

Subjects will be contacted by phone at 4 weeks after enrollment (Phone call). Assessments conducted during this visit include:

- Interim medical history including need for antibiotics and/or steroids for a respiratory event including review of smoking status.
- Concomitant medications (See Note).
- Assessment of medication side effects
- Evaluate for interim acute exacerbation

7.7 End of Study (all subjects, Visit 2)

Subjects will be brought in to the clinical center for their second study visit at week 12 Assessments conducted during this visit will include:

- Concomitant medications.
- Interim medical history including need for antibiotics and/or steroids for a respiratory event and review of smoking status.
- Current and prior COPD medication history used in the 12 weeks since Visit 1

- Physical Exam and vital signs
- Completion of questionnaires including SGRQ, CAT and TDI
- FEV_1, FVC, SVC and IC before administration of study drug and FEV_1 and FVC every hour after administration of study drug for a total of three hours (i.e. a trough and an AUC_{0-3} measurement).
- Evaluate for interim acute exacerbation
- Indacaterol/glycopyrrolate capsule counts
- Collection of diary cards
-

7.8 Schedule of Events for Participants Requiring No Medication Washout

	Pre-Screen Phone Visit	Screen/ Enrollment Visit 1	Phone Call	End of Study[3] Visit 2
Study Week	≤ - 4	0	4	12
Study Day	-30 to -1	0	28	84
Window (in days)		0	±7	±7
Informed consent		X		
Review of inclusion and exclusion criteria	X	X		
Demographics		X		
Baseline Medical history		X		
Smoking history/status	X	X	X	X
Physical exam including HR and BP		X		X
FEV_1, FVC, SVC and IC before and 15 mins after 4 puffs of albuterol		X		
FEV_1, FVC, SVC and IC before administration of study drug and FEV_1 and FVC every hour after administration of study drug for a total of three hours (i.e. a trough and an AUC_{0-3} measurement).				X
Research Labs - Pregnancy test[1], Potassium Level Check[4]		X		
CAT	X	X		X
SGRQ		X		X
BDI/TDI [2]		X		X
Review interim medical history			X	X
Review concomitant meds	X	X	X	X
Distribution of daily diary		X		
Collection of daily diary				X
Drug distribution		X		

Smoking cessation education		X[5]		
Capsule counts				X

1. Females of childbearing potential are required to have a negative pregnancy test prior to randomization.
2. BDI done at Screening /Enrollment visit, TDI done at Visit 2.
3. Should a subject terminate early, the subject will be brought in to complete all assessments included at the Week 12 End of Study visit.
4. Serum potassium level check either at the enrollment visit or at a separate screening visit. The serum potassium level must be available and reviewed before randomization.
5. Current smokers only

7.9 Schedule of Events for Participants Requiring Washout

	Pre-Screen Phone Call	**On-Site Wash-out Visit 0**	**Phone Call**	**Screen/ Enroll-ment Visit 1**	**Phone Call**	**End of Study[3] Visit 2**
Study Week	-8 to -4		≤ -1	0	4	12
Study Day	-60 to -31	-30 or more	-7 to -1	0	28	84
Window (in days)					±7	±7
Informed consent		X				
Review of inclusion and exclusion criteria	X	X		X		
Demographics		X				
Baseline Medical history		X				
Smoking history/status	X	X		X	X	X
Physical exam including HR and BP		X		X		X
FEV_1 and FVC 15 mins after 4 puffs of albuterol		X				
FEV_1, FVC, SVC and IC before and 15 mins after 4 puffs of albuterol				X		
FEV_1, FVC, SVC and IC before administration of study drug and FEV_1 and FVC every hour after administration of study drug for a total of three hours (i.e. a trough and an AUC_{0-3} measurement).						X
Research Labs - Pregnancy test[1], Potassium Level Check[4]				X		
CAT	X	X		X		X
SGRQ				X		X
BDI/TD[2]				X		X
Review interim medical history			X	X	X	X
Review concomitant meds	X	X	X	X	X	X

Distribution of daily diary				X		
Collection of daily diary						X
Drug distribution				X		
Smoking cessation education		X[5]				
Capsule counts						X

1. Females of childbearing potential are required to have a negative pregnancy test prior to randomization.
2. BDI done at Screening/ Enrollment visit, TDI done at Visit 2.
3. Should a subject terminate early, the subject will be brought in to complete all assessments included at the Week 12 End of Study visit.
4. Serum potassium level check either at the enrollment visit or at a separate screening visit. The serum potassium level must be available and reviewed before randomization.
5. Current smokers only

7.10 Unscheduled Visits

If disease activity increases or other concerns arise between regularly scheduled visits, participants should be instructed to contact study personnel and may be asked to return to the study site for an “unscheduled” visit. For individuals who are considered a “treatment failure” defined by increase in lower respiratory symptoms necessitating treatment with active, long-acting inhaled bronchodilator, inhaled or oral corticosteroids, or antibiotics, every effort will be made to bring the individual back for a study visit at the time of treatment failure to assess safety and for a final study visit as close to 12 weeks as possible.

7.11 Visit Windows

Study visits should take place within +/- 7 days of the schedule outlined in the schedule of events. If an acute exacerbation of COPD delays visit 2, then this visit may occur after clinical stabilization and beyond 7 days. If the delay causes subject to run out of study medication, contact the DCC for further instructions.

7.12 Discontinuation of study treatments

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason. If premature withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a patient’s premature withdrawal from the study and record this information on the Study Completion eCRF. Patients who discontinue study drug before completing the study, and those who prematurely withdraw from the study for any reason, an attempt should be made to schedule the subjects for a final visit as close to 12 weeks as possible.

Study treatment must be discontinued and the patient withdrawn from the trial under the following circumstances:

a. Withdrawal of informed consent
b. Pregnancy
c. Any other protocol deviation that results in a significant risk to the patient’s safety
d. For patients who are lost to follow-up (i.e. those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.
e. Patients who are prematurely withdrawn from the study will not be replaced by an equal number of newly enrolled patients.

f. Discretion of the site primary investigator.

7.13 Special Consideration(s) for Treatment Failure Subjects

Treatment failure is defined as an increase in lower respiratory symptoms necessitating treatment with long acting bronchodilator, corticosteroids or antibiotics.

If any new inhaled respiratory medication (other than Albuterol), antibiotic, or oral steroid was started for lower respiratory symptoms (NOT sinusitis), patient has met treatment failure endpoint. The subject should be encouraged to remain in the study and on study drug, unless started on an open label long-acting bronchodilator. For treatment failure subjects where study medication is discontinued, the full End of Study Spirometry 0-3 AUC should NOT be performed. Rather only one pre-BD FEV_1, FVC, SVC and IC should be performed.

ALL subjects who experience treatment failure should continue with the study through to completion. Subjects who require treatment with a prohibited COPD medication (Table 4.3-2) shall discontinue study drug and NOT re-start study drug.

Subjects who meet treatment failure AND who discontinue drug will perform a modified pulmonary function assessment at the end of study visit (Week 12). Refer to the study Manual of Operations for further details.

7.13.1 Special Consideration(s) for subjects who start a prohibited medication (Table 4.3-1)

Subjects who begin treatment with a prohibited medication (Table 4.3-1) shall discontinue study drug and NOT re-start study drug. These subjects will perform a modified pulmonary function assessment at the end of study visit (Week 12). Refer to the study Manual of Operations for further details.

7.13.2 Special Consideration(s) for subjects who experience an AE/SAE requiring study drug interruption

Subjects that have stopped taking study drug due to an adverse event may re-start taking study drug after recovery. In all instances the timing of re-starting study drug is left to the discretion of the site Primary Investigator.

Note that adverse events requiring treatment with a COPD-prohibited medication (4.3.2) meet the definition for treatment failure. These individuals shall not restart study drug.

Additionally, these subjects will perform a modified pulmonary function assessment at the end of study visit (Week 12). Refer to the study Manual of Operations for further details.

8. Safety Monitoring and Reporting

8.1 Overview

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data. Adverse events that are classified as serious according to the definition of health authorities must be reported promptly (per Section 12.5, *Reporting of Serious Adverse Events and Adverse Events*). Appropriate notifications will also be made to site principal investigators, Institutional Review Boards (IRBs) and DCC. Information in this section complies with *ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6: Guideline for Good Clinical Practice*, 21CFR Parts 312 and 320, and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE) : http://ctep.cancer.gov/reporting/ctc.html.

8.2 Definitions

8.2.1 Adverse Event (AE)

Any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice) (from OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (1/15/07)" http://www.hhs.gov/ohrp/policy/advevntguid.html#Q2)

For this study, an adverse event will include any untoward or unfavorable medical occurrence associated with:

- **Study therapy regimen**: Occurring within one week of use of indacaterol/glycopyrrolate.

- **Study mandated procedures**: Any event occurring within one day of a mandated study procedure will be considered a possible adverse event of these procedures and will be evaluated further for any relationship. These procedures include spirometry.

For the procedures below, clinical situations are listed that are considered to be outside the normal range of outcomes and will be recorded as Adverse Events. These situations do not limit an investigator from recording and reporting any other events, associated or not with these procedures as AEs.

Pulmonary Function Testing

- Wheezing, shortness of breath or chest tightness requiring treatment with bronchodilators within 30 minutes from the procedure
- Coughing requiring treatment with bronchodilators within 30 minutes from the procedure

8.2.1.1 Suspected Adverse Reaction (SAR)

Any adverse event for which there is a reasonable possibility that the investigational drug caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (21 CFR 312.32(a)).

8.2.2 Unexpected Adverse Event

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the package insert or is not listed at the specificity, severity or rate of occurrence that has been observed; or is not consistent with the risk information described in the protocol.

8.2.3 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator it results in any of the following outcomes (21 CFR 312.32(a)):

1. Results in death;
2. Is life-threatening i.e. places a participant at immediate risk of death from the event as it occurred;
3. Requires inpatient hospitalization or prolongation of existing hospitalization;
4. Results in a persistent or significant disability/incapacity;
5. Results in a congenital anomaly/birth defect; OR
6. Any other adverse event that, based upon appropriate medical judgment, may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (*e.g. allergic bronchospasm requiring intensive treatment in the emergency room or at home*).

Elective hospitalizations or hospital admissions for the purpose of conduct of protocol mandated procedures are not to be reported as an SAE unless hospitalization is prolonged due to complications.

8.3 Grading and Attribution of Adverse Events

8.3.1 Grading Criteria

The study site will grade the severity of adverse events experienced by the study participants according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0) This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events. The NCI-CTCAE has been reviewed by the Protocol Chairs and has been deemed appropriate for the subject population to be studied in this protocol.

Grade 1 = mild adverse event.

Grade 2 = moderate adverse event.

Grade 3 = severe and undesirable adverse event.

Grade 4 = life-threatening or disabling adverse event.

Grade 5 = death.

Events of grade 2 or higher will be recorded on the appropriate electronic AE case report form for this study. If a specific event or result from a given clinical evaluation is not included in the NCI-CTCAE manual, then an abnormal result would be considered an adverse event if changes in therapy or monitoring are implemented as a result of the event/result.

8.3.2 Attribution Definitions

The relationship, or attribution, of an adverse event to the study therapy regimen or study procedure(s) will initially be determined by the site investigator and recorded on the appropriate AE eCRF. The relationship of an adverse event to study therapy regimen or procedures will be determined using the descriptors and definitions provided in Table 8.3.2.

For additional information and a printable version of the NCI-CTCAE manual, consult the NCI-CTCAE web site: http://ctep.cancer.gov/reporting/ctc.html.

Table 8.3.2 Attribution of Adverse Events

Code	Descriptor	Relationship (to primary investigational product and/or other concurrent mandated study therapy or study procedure)
RELATED CATEGORIES		
1	Definitely	The adverse event is clearly related.
2	Probably	There is evidence to suggest a probable causal relationship.
3	Possibly	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
UNRELATED CATEGORY		
4	Not related	The adverse event is clearly not related.

8.4 Collection and Recording of Adverse Events

8.4.1 Collection Period

Adverse events will be collected from the time of consent until a subject completes study participation or until 30 days after he/she prematurely withdraws (without withdrawing consent) or is withdrawn from the study.

8.4.2 Collecting Adverse Events

Adverse events (including SAEs) may be discovered through any of these methods:

- Observing the subject.
- Interviewing the subject [e.g., using a checklist, structured questioning, diary, etc.] .
- Receiving an unsolicited complaint from the subject.
- In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an adverse event, as defined in Section 8.3, *Grading and Attribution of Adverse Events.*

8.4.3 Recording Adverse Events

Throughout the study, the investigator will record adverse events and serious adverse events as described previously (Section 8.2, *Definitions)* on the appropriate eCRF regardless of the relationship to study therapy regimen or study procedure.

Once recorded, an AE/SAE will be followed until it resolves with or without sequelae, or until the end of study participation, or until 30 days after the subject prematurely withdraws (without withdrawing consent)/or is withdrawn from the study, whichever occurs first.

8.5 Reporting of Serious Adverse Events and Adverse Events

8.5.1 Reporting of Serious Adverse Events

Each adverse event is to be classified by the investigator as serious (see Section 8.2.3, Serious Adverse Event) or non-serious. This classification determines the reporting procedures to be followed. If a serious adverse event occurs, expedited reporting to local regulatory bodies will follow local regulations as appropriate. The site investigator will report to protocol chairs and the DCC all serious adverse events (see Section 8.2.3, Serious Adverse Event), regardless of relationship to study drug or expectedness within 24 hours of discovering the event.

SAEs are reportable from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the clinical trial, i.e., prior to undergoing any trial-related procedure and/or receiving investigational product, until a subject completes study participation or until he/she prematurely withdraws or is withdrawn from the study.

For serious adverse events, all requested information on the AE/SAE eCRF should be provided. In particular, if the serious adverse event is fatal or life-threatening, notification to the DCC must occur immediately. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports. In the event that the investigator does not become aware of the occurrence of a serious adverse event immediately (e.g., if an outpatient trial subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event. As additional details become available, the AE/SAE eCRF will be updated and submitted. When an SAE report is sent it will include the PIs assessment of the adverse event and assignment of a relationship to any specific aspect of the study. In addition, an investigator may be requested to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the DCC or its designated representative. The investigator's assessment of causality must be provided. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an adverse event. If the

investigator's causality assessment is "unknown but not related to study drug", this should be clearly documented on study records. In addition, if the investigator determines the adverse event is associated with trial procedures, the investigator must record this causal relationship in the source documents and eCRF, as appropriate.

8.5.2 Reporting to Health Authority

After an adverse event requiring 24 hour reporting (per Section 8.5.1, *Reporting of Serious Adverse Events*), the event will be submitted by the site investigator and assessed by protocol chairs and the DCC per local regulations. Although this protocol was submitted to the FDA and received an IND exemption, MedWatch forms will be completed for applicable Serious Adverse Events and forwarded to Sunovion Pharmaceuticals (global oversight for the study) for further reporting to the FDA.

8.5.2.1 Annual Reporting

The investigator will include in the annual study report to local regulatory authorities all adverse events classified as:

- Serious and unexpected suspected adverse reaction (see Section 8.2.1.1, Suspected Adverse Reaction, and Section 8.2.2, Unexpected Adverse Event).
- Serious adverse reaction that is not suspected to be related to the treatment (see Section 8.2.2, Suspected Adverse Reaction).

Pregnancies are not reported as serious adverse events.

The DCC will receive a copy of the annual study report submitted by the investigator to the local regulatory authorities. The investigator shall also summarize safety data at the end of the study and periodically throughout the study for the DSMB. These reports may include (but are not limited to) masked summaries and listings of AEs, SAEs, events requiring discontinuation of a study-mandated procedure for individual subjects and protocol deviations. All adverse events (not just those requiring 24-hour reporting) will be reported by the protocol chairs and the DCC to the DSMB.

8.5.2.2 Expedited Safety Reporting

Serious and unexpected suspected adverse reaction [SUSAR] (see Section 8.2.1.1, *Suspected Adverse Reaction* and Section 8.2, *Unexpected Adverse Event* and 21 CFR 312.32(c)(1)i).

The investigator shall report any suspected adverse reaction that is both serious and unexpected. The investigator shall report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study drug and the adverse event, such as:

1. A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, or Stevens-Johnson Syndrome);
2. One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
3. An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

SAEs that are unexpected will be reported to the DSMB by the protocol chairs and the DCC within 15 calendar days of their notification of the event. If a death or life-threatening event occurs that is believed by the site investigator to be study drug related, notification to the DSMB by the protocol chairs and the DCC will occur

within 7 calendar days after their initial notification of the event. Copies of the Expedited Safety Report will also be provided to the site investigators.

8.5.3 Reporting of Adverse Events to IRBs/IECs

The investigator shall report adverse events, including expedited reports, in a timely fashion to their respective IRBs/IECs in accordance with applicable local regulations and guidelines.

8.6 Reporting of Other Safety Information

An investigator shall promptly notify the site IRB as well as the DCC when an "unanticipated problem involving risks to participants or others" is identified, which is not otherwise reportable as an adverse event.

8.7 Review of Safety Information

8.7.1 DCC Adverse Event Review

The DCC shall receive annual reports from the protocol investigator compiling new and accumulating information on AEs, SAEs, and pregnancies recorded by the study site on appropriate eCRFs. The Protocol Chairs will also review SAE and pregnancy reports in real time.

8.7.2 DSMB Review

8.7.2.1 Planned DSMB Reviews

The Data and Safety Monitoring Board (DSMB) shall review safety data at least yearly during planned DSMB Data Review Meetings. Data for the planned safety reviews will include, at a minimum, a listing of all reported AEs and SAEs. The DSMB will be informed of any Expedited Safety Reports in a timely manner. Reports will be prepared by the DCC and will be sent to the DSMB for their regular scheduled meetings. Tables showing study progress will be presented by clinical center and overall. These will minimally include recruitment, protocol deviations, adherence, attrition, adverse events, data quality, descriptive characteristics of the study sample, and efficacy. All AEs will be reported as described above.

8.7.2.2 *Ad hoc* DSMB Reviews

In addition to the pre-scheduled data reviews and planned safety monitoring that will be coordinated by the DCC, the DSMB may be called upon for *ad hoc* reviews. The DSMB will review any event that potentially impacts safety at the request of the Protocol Chairs or the DCC. In addition, the following events will trigger an *ad hoc* comprehensive DSMB Safety Review:

- Any death that occurs in the study, which is possibly or definitely related to study treatment regimen.
- The occurrence of a Grade 3 or higher related and unexpected SAE in any study participants who have received a study treatment.

After review of the data, the SMC will make recommendations regarding study conduct and/or continuation.

8.7.2.2.1 Temporary Suspension of enrollment for *ad hoc* DSMB Safety Review

A temporary halt in enrollment will be implemented if an *ad hoc* DSMB safety review is required. No new participants will be enrolled until the DSMB has met and discussed the eCRFs.

9. Statistical Considerations and Analytical Plan

9.1 Overview

The scientific objective of this study is to determine whether the combination of long-acting beta agonist, indacaterol, and the long-acting muscarinic antagonist, glycopyrrolate, provides symptom relief and improves

clinical status in symptomatic smokers with post-BD $FEV_1/FVC \geq 0.70$, a group of patients that has not previously been objectively evaluated in a placebo-controlled trial. The study design is a two-visit study of 580, symptomatic current or former smokers who will be randomized in a double-blind, placebo-controlled fashion to indacaterol/glycopyrrolate versus placebo. "Symptomatic" for the purposes of this study will be defined as CAT score≥10. During the first visit, baseline SGRQ score will be established and the subject assigned to drug versus placebo. SGRQ score will be reassessed at the second in-person visit. Treatment failure during the study period will be defined by increase in lower respiratory symptoms necessitating treatment with active, long-acting inhaled bronchodilator, inhaled or oral corticosteroids, or antibiotics.

9.2 Endpoints/Outcomes

The primary scientific endpoint of this study is the proportion of subjects who experience a four point drop in SGRQ in the treatment versus placebo groups and do not meet criteria for treatment failure during the 12 week treatment period. The rationale for this composite definition of "success" with respect to the primary outcome is that differential treatment failure in the two arms could bias the observed change in SGRQ at 12 weeks if subjects who are randomized to placebo fail inordinately and are more likely to receive a long-acting bronchodilator or corticosteroid and cease study medication during the 12 week treatment period. In other words, we will not consider participants who have treatment failure during the study as eligible for "success" at the end of the study. Instead, they will be considered a "failure" with respect to the primary outcome regardless of their SGRQ score at 12 weeks. This will also allow us to avoid a major source of non-ignorable missing data due to "drop outs" and lack of data on SGRQ score at 12 weeks. If those drop outs occurred because of treatment failure, then they will still add to our primary outcome because they will meet criteria for "failure".

Key Secondary endpoints include:

a. Proportion of subjects in the treatment versus placebo groups who experience a two point improvement in CAT score without treatment failure.
b. Proportion of subjects in the treatment versus placebo groups who experience a one unit improvement in BDI/TDI score without treatment failure.
c. Mean change in SGRQ
d. Mean change in CAT
e. Mean change in BDI/TDI
f. $AUC_{0\text{-}3h}$ for FEV_1
g. Mean 12-week change in trough FEV_1 between treatment and placebo groups (absolute and % predicted).
h. Mean 12-week change in trough Inspiratory Capacity, FEF25-75% and iso-volume FEF25-75%between treatment and placebo groups (absolute and % predicted).
i. Mean change in symptoms and rescue medication use based on daily diary.
j. Treatment failure defined by increase in respiratory symptoms necessitating treatment with active, long-acting inhaled bronchodilator and/or corticosteroid (inhaled or oral).

9.3 Measures to Minimize Bias

A stratified, randomized block procedure will be used where strata are defined by clinical center, smoking status and history of prior treatment with COPD maintenance medication.

9.4 Analysis Plan

9.4.1 Analysis Populations.

9.4.1.1 Safety Population

The Safety Population is defined as all subjects who have consented to participate. The Safety Population will be used for all safety analyses. Subjects will be analyzed by treatment received. If subjects inadvertently receive both active drug and placebo, they will be included in the indacaterol/glycopyrrolate group.

9.4.1.2 Efficacy Populations

The primary outcome will be based on intention-to-treat population for the SGRQ measurement which will be supplemented by blinded assessment of treatment failure in a composite endpoint. For individuals who do not complete 12 weeks of treatment, every effort will be made to bring them back at 12 weeks for SGRQ and other symptom and physiologic assessments. For those who drop out of the study and decline any further visits, we will compare baseline values to those who complete the 12 week assessments and note any differences that could impact the analysis.

9.4.1.3 Effect of drop outs on the Efficacy population

Our composite primary endpoint definition will allow us to avoid a major source of missing data due to "drop outs" and lack of data on SGRQ score at 12 weeks. If those drop outs occurred because of treatment failure (which may be disease-related and intervention-related), then they will still be "informative" in that they add to our primary outcome because they will meet criteria for "treatment failure". There will remain some drop outs that are "non-informative" because they are due to factors other than treatment failure. This number should be small given our relatively short study and should be due to random causes that are unrelated to the disease or the intervention. Subjects with non-informative missing measures at 12 weeks will not be included in the analysis.

9.4.2 Primary Analysis of Primary Endpoint(s)/Outcome(s)

The primary analysis will be conducted via GEE regression with logit link to compare the proportion of subjects who experience improvement with treatment defined as a four point drop in SGRQ and absence of treatment failure in the treatment versus placebo groups, adjusted for clinical center of recruitment, change of smoking status between baseline and 12 weeks, prior maintenance treatment for COPD requiring washout, and BMI at baseline. No formal statistical analysis for efficacy will be conducted until the end of the study given the interest in obtaining follow-up for multiple endpoints of interest. Change of Smoking status will be modeled as a categorical variable with four categories reflecting the four potential types of changes patients might experience (persistent smoker, persistent former smoker, smoker quit smoking during the trial, former smoker restarts smoking during the trial). Baseline BMI will be included as a continuous variable.

Denote Δ $SGRQ_{ij}$ be the change of SGRG between baseline and 12 weeks for subject *j* (j=1,2,3,..n_i) from site I (i=1, 2,3…, m).

If Δ $SGRQ_{ij}$ ≥4 and no trt failure, let Y_{ij}=1, otherwise Y_{ij}=0. The model we will use is as the following:

$\text{logit}\{Pr(Y_{ij}=1)\}= \beta_1+\beta_2\text{Treatment}_{ij}+\beta 3\text{Change of Smoking Status}_{ij}+\beta 4\text{Washout}_{ij}+\beta_5\text{BMI}_{ij}$
Within site association among the response will be modeled by exchangeable correlation structure.

9.4.3 Supportive Analyses of the Primary Endpoint(s)/Outcome(s)

To address the potential heterogeneity our study population, additional planned supportive analyses will be to examine the primary endpoint in specific subgroups based on smoking status (current smoker yes/no), long-term respiratory medication use prior to entering the study requiring washout and baseline bronchodilator

responsiveness and BMI (males with BMI >30kg/m^2, males with BMI ≤30kg/m^2, females with BMI >30kg/m^2, females with BMI ≤30kg/m^2). Additional exploratory subgroup analyses will also include gender (male/female), age (<65 years/≥65 years), baseline FEV_1% predicted baseline IC (< median for all randomized subjects / ≥ median for all randomized subjects), presence of chronic bronchitis, Interactions between these covariates and treatment will be tested to study whether treatment effect on primary outcome differs between corresponding subgroups. If interaction term is found to be significant, additional analysis will be done to study treatment effect within each subgroups. Each covariate will be tested one at a time.

9.4.4 Analyses of Secondary and Other Endpoint(s)/Outcome(s)

As outlined for analysis of the primary endpoint, a similar GEE regression will be conducted to compare the proportion of subjects who experience a 2 point drop in CAT without treatment failure, a 1 point drop in TDI without treatment failure and treatment failure alone in the treatment versus placebo groups adjusted for clinical center and smoking status. For analysis of continuous measures including 12-week change in trough FEV_1, trough Inspiratory Capacity, FEF25-75% and iso-volume FEF25-75% and $AUC_{0\text{-}3h}$, analysis will be conducted with linear mixed models to adjust for center effect. No adjustment for multiplicity will be made.

9.4.5 Additional Analyses

Regression models with multivariable will also be used to adjust the secondary endpoints for baseline covariates of interest including age, gender, smoking status, 12-hour trough FEV_1%, 12-hour trough IC, bronchodilator responsiveness, BMI and history of long-term respiratory medication use.

9.5 Interim Analyses

9.5.1 Interim Analysis of Efficacy Data

None

9.5.2 Interim Analysis of Safety Data

Safety Analyses

Safety analyses will be performed on the Safety Population biannually or when 100 patients have completed 12 weeks of follow-up, whichever is sooner.

Safety Assessments

The following assessments will be used to monitor safety:

- Adverse events (AEs) and serious adverse events (SAEs)
- Changes in FEV_1 between baseline and twelve weeks for all randomized study subjects.

Planned Method of Analysis

Safety data will be summarized descriptively overall and separately for the active treatment group, placebo group, and consented but not randomized subjects. Individual subject listings will be prepared for all safety data.

Adverse Events

Frequencies (number and percentage) of subjects with one or more treatment emergent AEs will be summarized by treatment group, by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA™) terminology. All treatment emergent AEs, all treatment emergent AEs potentially related to study drug, all treatment emergent SAEs and all treatment emergent SAEs potentially related to study drug will be summarized. Specific AEs of special interest, particularly respiratory system related AEs, will be outlined in the SAP and summarized.

The incidence of AEs, and their severity, as well as the incidence of subjects who withdraw due to an AE will be tabulated. A subject listing of all treatment emergent AEs, and AEs causing study discontinuation will be presented.

Changes in FEV_1

Summary statistics (mean, standard deviation, minimum, and maximum) in changes in FEV_1 will be tabulated for the overall randomized population and by treatment group (labeled as 'A' and 'B').

9.6 Statistical Hypotheses

The superiority of indacaterol/glycopyrrolate over placebo will be evaluated by testing the following null hypothesis (Ho) versus the alternative hypothesis (Ha):

Ho: There is no difference in the proportion of individuals with a 4 point drop in SGRQ after 12 weeks of treatment for patients with symptomatic, smokers with post-BD FEV_1/FVC ≥0.70 treated with indacaterol/glycopyrrolate compared to placebo.

Ha: There is a difference in in the proportion of individuals with a 4 point drop in SGRQ after 12 weeks of treatment for patients with symptomatic, smokers with post-BD FEV_1/FVC ≥0.70 treated with indacaterol/glycopyrrolate compared to placebo.

9.7 Sample Size Considerations

Sample size estimations were performed using preliminary data from the Novartis FDA development program studies. At week 12, using Flight 1 where the effect on SGRQ was slightly smaller than Flight 2, 57% of subjects taking indacaterol/glycopyrrolate vs 39% of subjects taking placebo had a ≥4 unit decrease in SGRQ. Using these data we estimate (with a two-sample test of proportions) that 290 subjects per arm would provide 90% power with the following assumptions: (1) a type I error rate of .05; (2) 10% loss to follow-up and (3) approximately 20% lower effect size given the Flight studies were based on a more severe patient population. Our primary analysis will define "response" as both a ≥4 unit decrease in SGRQ and an absence of treatment failure during the 12 week treatment period. This additional requirement is designed to protect against bias towards the null that would occur if subjects randomized to placebo have a greater number of treatment failures and thus a greater number of subjects who are switched to active drug during the study. We do not have data available on the effect size of bronchodilators in the GOLD 0 population or the specific effect that our composite outcome (including the treatment failure definition) will have. However we believe that a sample size estimate using this approach should provide a realistic estimate of power given that we are assuming a lower effect size and protecting against bias towards the null result.

10. Identification and Access to Source Data

10.1 Source Data

Source documents and source data are considered to be the original documentation where subject information, visits consultations, examinations and other information are recorded. Documentation of source data is necessary for the reconstruction, evaluation and validation of clinical findings, observations and other activities during a clinical trial.

10.2 Access to Source Data

The site investigators and site staff will make all source data available to the DCC as well as to relevant health authorities. Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals.

11. Protocol Deviations

11.1 Protocol Deviation Definitions

Protocol Deviation – The investigators and site staff will conduct the study in accordance to the protocol; no deviations from the protocol are permitted. Any change, divergence, or departure from the study design or procedures constitutes a protocol deviation. As a result of any deviation, corrective actions will be developed by the site and implemented promptly.

Major Protocol Deviation (Protocol Violation) - A Protocol Violation is a deviation from the IRB approved protocol that may affect the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. In addition, protocol violations include willful or knowing breaches of human subject protection regulations, or policies, any action that is inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles, and a serious or continuing noncompliance with federal, state, local or institutional human subject protection regulations, policies, or procedures.

Non-Major Protocol Deviation - A non-major protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that does not have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

11.2 Reporting and Managing Protocol Deviations

The study site principal investigator has the responsibility to identify, document and report protocol deviations as directed by the study Sponsor. However, protocol deviations may also be identified during site monitoring visits or during other forms of study conduct review. Upon determination that a protocol deviation has occurred, the study staff will a) notify the site Principal investigator, b) notify the DCC and the Protocol Chairs, c) will complete a Protocol Deviation eCRF, d) and report the deviation to the local regulatory authorities. The Protocol Chairs and the DCC will make the decision as to whether the deviation is major or not and what the impact of the deviation on the study participant or the entire study may be. Protocol Deviations will also be reported by the Protocol Chairs and the DCC and DSMB.

11.3 Ethical Considerations and Compliance with Good Clinical Practice

11.4 Statement of Compliance

This clinical study will be conducted using good clinical practice (GCP), as delineated in *Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance*, and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by the IRB. Any amendments to the protocol or to the consent materials will also be approved by the IRB before they are implemented.

11.5 Informed Consent Process

The consent process will provide information about the study to a prospective participant and will allow adequate time for review and discussion prior to his/her decision. The principal investigator or designee listed on the Investigator of Record form, will review the consent and answer questions. The participant will have the option to speak to the principal investigator for any questions regarding the study and consent. The prospective participant will be told that being in the trial is voluntary and that he or she may withdraw from the study at any time, for any reason. All participants (or their legally acceptable representative) will read, sign, and date a consent form before undergoing any study procedures. Consent materials will be presented in English and a copy of the signed consent form will be given to the participant. The consent form will be revised when important new safety information is available, the protocol is amended, and/or new information becomes available that may affect participation in the study.

11.6 Privacy and Confidentiality

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique identification number and these numbers rather than names will be used to collect, store, and report participant information. Site personnel will not transmit documents containing personal health identifiers (PHI) to the study sponsor or their representatives.

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