Investigator-Initiated Trial (IIT)
Product: Indacaterol 110 µg/Glycopyrronium 50 µg (Ultibro®) and Tiotropium 18 µg (Spiriva®)
Indication: Moderate to severe COPD
Country: Canada
Sponsor: Novartis
Principal Investigator (PI): François Maltais, IUCPQ, Québec City

Has the Principal Investigator conducted IITs supported by Novartis?
YES NO X

Title of study: Indacaterol 110 µg/Glycopyrronium 50 µg (Ultibro®) versus Tiotropium 18 µg (Spiriva®) alone to reduce exertional dyspnea in patients with moderate to severe COPD. **The RED Trial**

Study Rationale
Long-acting bronchodilators such as tiotropium, salmeterol, formoterol, aclidinium, indacaterol and glycopyrronium are effective in improving cycling exercise tolerance in COPD[1-7]. In well-designed, randomized, placebo controlled trials, these bronchodilators have been convincingly shown to reduce operating lung volume at rest and during exercise and to improve the endurance time to submaximal cycling exercise in COPD. For a given exercise stimulus, long-acting β2-agonists (LABA) and long acting muscarinic antagonist (LAMA) also reduce the perception of dyspnea[1-4].

The foundation of COPD therapy is to combine inhaled therapy to optimize benefits as it was done several years ago by associating short-acting β2-agonists and muscarinic antagonist[8]. The recent availability of once-daily LABA/LAMA fixed combination products makes this therapeutic strategy even more appealing and appears as a promising treatment option in COPD. One relevant question regarding these new LABA/LAMA combinations is whether they provide superior benefits compared to a single agent. Once-daily LABA/LAMA fixed combinations consistently improves lung function compared to monotherapy[9-12]. The key question is whether they provide superior efficacy to monotherapy on patient's oriented clinical outcomes, beyond lung function improvement. In regards, once-daily LABA/LAMA fixed combinations can reduce exacerbation rate[11] and perception of dyspnea[13], further to what can be obtained with the monocomponents. Once-daily LABA/LAMA fixed combinations also improve exercise tolerance compared to placebo but whether they provide additional benefit over monotherapy is uncertain[14-16].

Dyspnea is the most troublesome symptom in COPD and it is felt that the main mechanism through which bronchodilators improve exercise tolerance is by reducing dyspnea[1,17]. As such, dyspnea measurement appears a valid surrogate of exercise tolerance. One advantage of dyspnea measurement over the measurement of exercise endurance is that it does not require a maximal effort. In this regard, it may be a less *noisy* outcome than exercise duration. Dyspnea can be quantified during the 6-min walking test but pre and post-intervention comparisons are made difficult since the walking speed and thus the exercise stimulus is not controlled during the test. Another strategy to evaluate the effects of interventions on exertional dyspnea is to compare

dyspnea at isotime while controlling the walking or cycling speed during the endurance shuttle walking test[18] or the constant rate cycling test[1,3](endurance test). One limitation of this approach is that pre and post intervention dyspnea measurement is not always obtained at the same time point since the duration of the test is variable. To overcome this problem, linear interpolation can be used to estimate dyspnea. However, this approach is not as robust as when a "real" dyspnea score is directly obtained from the patients.

To circumvent these difficulties, we have recently developed a strong and simple exercise methodology whose primary objective is to assess exertional dyspnea in patients with COPD: the 3-min constant speed shuttle test[19,20]. During this test, which is a modification of the endurance shuttle walking test, patients are asked to walk around two cones set-up in a flat corridor and separated by 10 meters. An audio signal is used to impose the walking speed and the test ends at a fixed duration of 3 minutes or until symptoms become intolerable. At pre-specified time point during the test, and at the end of the test (3 min), patients are asked to score their perception of dyspnea on a 10-point modified Borg scale. The feasibility and reproducibility of this test in providing a standardized physical stimulus and a measurable level of dyspnea in patients with moderate to severe COPD has been reported[19]. In one study, we also confirmed the responsiveness of this test to bronchodilation, reporting statistically and clinically significant reduction in modified Borg scale dyspnea score with ipratropium bromide compared to placebo[20].

Based on these considerations, the proposed trial will compare the effectiveness of dual (Indacaterol 110 µg/Glycopyrronium 50 µg [Ultibro®]) versus single (Tiotropium 18 µg [Spiriva®]) bronchodilation to reduce exertional during the 3-min constant speed shuttle test in patients with moderate to severe COPD.

Objectives

Primary objective

To compare the reduction in modified Borg scale dyspnea score during the 3-min constant speed shuttle test after 3 weeks of indacaterol 110 µg/Glycopyrronium 50 µg (Ultibro®) versus Tiotropium 18 µg (Spiriva®) alone in patients with moderate to severe COPD.

Hypothesis

Indacaterol 110 µg/Glycopyrronium 50 µg (Ultibro®) will provide superior reduction in dyspnea during the 3-min constant speed shuttle test than Tiotropium 18 µg (Spiriva®) alone in patients with moderate to severe COPD.

Secondary objectives

To evaluate the impact of indacaterol 110 µg/Glycopyrronium 50 µg (Ultibro®) and Tiotropium 18 µg (Spiriva®) alone on pulmonary function and quality of life after 3 weeks of treatment in patients with moderate to severe COPD.

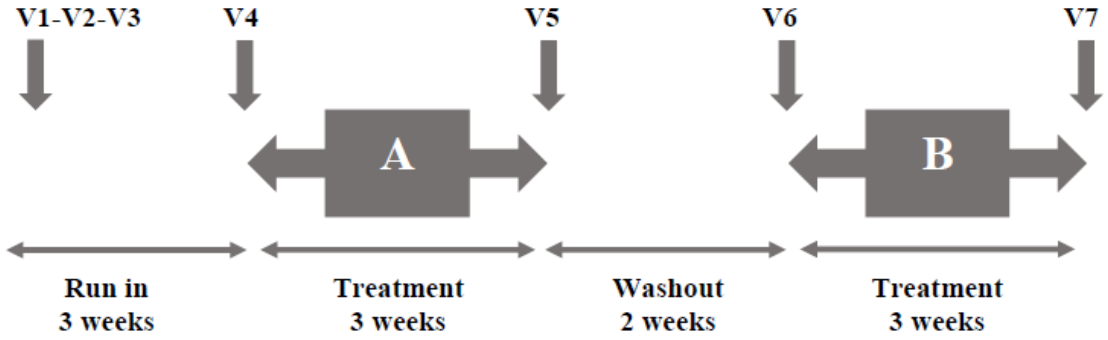
To evaluate the impact of indacaterol 110 µg/Glycopyrronium 50 µg (Ultibro®) and Tiotropium 18 µg (Spiriva®) alone on exertional dyspnea after the first dose of therapy in patients with moderate to severe COPD.

To do a prospective determination of the initial walking speed during the 3-min CSST.

Study Design

This will be a, randomized, double-blinded, cross-over trial.

Figure 1: Design Flow-chart



Methodology

The study will require 7 visits; the run-in and familiarization phase (visits #1-3), the treatment A phase (visits #4-5), and the treatment B phase (visits #6-7).

The first visit will be used to review the inclusion criteria and to obtain consent. Patients will be asked to perform a pulmonary function test including spirometry, lung volumes and diffusion capacity measurements. Patient on tiotropium, glycopyrronium, aclidinium, umeclidinium or any LAMA drugs will be switched to open label ipratropium (see allowed medication). At Visit#2 a progressive maximal exercise test will be obtained by performing the incremental shuttle walking test, the COPD assessment test (CAT) and the MRC scale will be also be completed. Patients will then be familiarized with the 3-min constant speed shuttle test. During Visit #3, patients will perform up to three 3-min constant speed shuttle test which will serve to determine dyspnea at baseline. We will aim for a dyspnea Borg Score > 3, the rationale being that it is important to obtain a significant dyspnea signal considering that the objective of the study is to evaluate the efficacy of bronchodilation to improve dyspnea. Patients in whom it will not be possible to achieve this level of dyspnea at the end of the 3-min constant speed shuttle test will be excluded for further study participation.

Patients will then enter the cross-over study design during which they will receive one of the two study treatments: indacaterol 110 µg/Glycopyrronium 50 µg (Ultibro®) once a day or Tiotropium 18 µg (Spiriva®) once a day. The treatment period will be three weeks. There will be a two-week washout period between the two treatment phases. Total study duration will thus be 11 weeks.

Visit #4 and Visit #6 will be the baseline visits for each treatment period (except for dyspnea after the 3-min constant speed shuttle test which will be determined at Visit #3). Patients will perform spirometry, lung volume measurements before and 1h 20 min after receiving the study medication. One 3-min constant speed shuttle test will be performed 2h25 min after dosing, starting with the one performed and completed at the highest

speed at Visit #3. This time schedule was chosen based on previous studies in this field[1,21]. Dyspnea will be assessed with the baseline dyspnea index (BDI)[22] and health status will be evaluated by the COPD Assessment Test (CAT)[23].

The same procedures will be repeated at the end of each three-week study treatment (Visits #5 and #7) the only difference being that chronic dyspnea will be assessed with the transitional dyspnea index (TDI).

Allowed medication
There will be a three-week run-in period during which patients will receive open label ipratropium (Atrovent® MDI 20 µg/ puff, 4 puffs QID) and prn salbutamol (Ventolin® MDI 100 µg/puff, 2 puffs every 3-4 hours prn). Ipratropium will be allowed only during the run-in and washout periods. Ipratropium will be stopped twelve hours before study visits (Visit # 2, #4, and #6).

Salbutamol on prn basis will be allowed throughout the study except that it will be stopped 6 hours prior to Visit #2, #4, #5, #6 and #7. Long-acting β2-agonist will be prohibited after Visit #1 and throughout study duration. Inhaled corticosteroids will be allowed at the same dosage as before the study. PDE4 inhibitors and leukotriene antagonists will also be allowed.

Population
Patients with moderate to severe COPD will be recruited for this study.

Key inclusion criteria
1) Age > 50 years
2) Smoking history > 10 packs/year
3) FEV_1 30 - 79% of predicted and FEV1/FVC < 70% (GOLD 2-3)
4) FRC > 120 % predicted
5) Borg dyspnea score > 3 during the 3-min constant speed shuttle test at Visit #3

Key exclusion criteria
1) Respiratory exacerbation within the 2 months preceding the study
2) Current diagnostic of asthma
3) Significant O_2 desaturation (SpO_2 < 85%) at rest or during exercise
4) Presence of another pathology that could influence exercise tolerance
5) Use of home oxygen

Number of centers & patients
Planned number of centers
Three centres will be necessary to complete the study.

Total number of patients
Based on a target dyspnea score of 5-6 during the placebo exercise and a standard deviation of 2[19,20] and looking for a change in dyspnea Borg score ≥ 0.75 with Indacaterol 110 µg/Glycopyrronium 50 µg (Ultibro®) versus Tiotropium 18 µg (Spiriva®), we calculated that 40 completed patients would be necessary to provide an α of 0.05 and a β

of 0.85. Expecting that 20% of screened patients will fail to reach a modified Borg dyspnea score > 3 during the 3-min constant speed shuttle test at baseline[20] and an attrition rate of 15% during the trial, we will recruit 60 patients into the study.

Investigational and Reference Therapy

# of Patients	Treatment Arm	Type of Study Drug	Compound	Dose	Freq.	Admin. Route
40 cross over design	Arm 1	Spiriva® handihaler	Tiotropium	18 µg	Daily 21 days	Inhalation
	Arm 2	Ultibro®	Indacaterol/ Glycopyrronium	110 µg/50 µg	Daily 21 days	Inhalation

Evaluation schedule: Timelines and Study duration

Table 1. Study visits

	Run-in and familiarization			Treatment A		Treatment B	
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Time of visit	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 6**	**Week 9**	**Week 11**
Inclusion/Exclusion criteria	X						
Information & consent	X						
Physical examination	X				X		X
Baseline dyspnea index (self-administered and computerized version) - BDI				X		X	
Transitional dyspnea index - TDI					X		X
CAT questionnaire		X		X	X	X	X
MRC score		X					
Spirometry	X	X		X	X	X	X
Lung volumes	X			X	X	X	X
DLCO	X						
Explanation of the ISWT	X						
ISWT		X					
Familiarization with 3-min CSST		X					
3-min CSST			X	X	X	X	X
Dispense study medication				X		X	
Adverse events					X		X

Randomization
Randomization stratified by site will occur at Visit #4 and will be centralized using a computerized system and pre-packaged study medication. The number display by the computer will be correlated to a numbered envelope which will contain a specified order of drug. The corresponding number and the treatment period will only be known by the assigned pharmacist responsible of the trial. This code will be broken only if there is a need for an emergency treatment and it will need to be authorized by the trial principal investigator.

Blinding
Patient and study staff will be blinded to the treatment administration during the 2 study periods. Treatments will consist, for one treatment period of active Ultibro® once a day and placebo Spiriva® handihaler, and for the other period of placebo Ultibro® once a day and active Spiriva® handihaler. Active medication and placebo will be of identical appearance and the order of study medication will be randomized. Pre-package envelopes containing equal quantities of inhaler combination will be numbered and kept in a secure place (pharmacy of the hospital or the research site). At the end of the study data collection the blind code will be opened after having completed the primary data analysis.

Compliance
Patients will be provided with 21 days (3 weeks) of numbered study inhalers each marked from Day 1 to Day 21. Compliance will be assessed by counting the returned empty inhalers. Administration of $\geq 80\%$ of the study medication will be determined as compliant.

Evaluation criteria
Primary endpoint will be the difference in modified Borg dyspnea score after the 3-min constant speed shuttle test after 3 weeks of treatment between indacaterol 110 µg/Glycopyrronium 50 µg (Ultibro®) versus Tiotropium 18 µg (Spiriva®) alone. Secondary endpoints will be the difference in modified Borg dyspnea score after the 3-min constant speed shuttle test after 3 weeks of treatment between indacaterol 110 µg/Glycopyrronium 50 µg (Ultibro®) versus baseline value (Visit #3) and between Tiotropium 18 µg (Spiriva®) alone versus baseline value (Visit #3). The dyspnea response after the first dose of therapy will also be assessed. The between-treatment differences in the improvement of pulmonary function (FEV1 and inspiratory capacity), TDI and CAT scores from baseline (Visit #4) to end of treatment period (Visit #5 and #7) will also be evaluated. Exploratory analyses will be performed on the cardio-pulmonary responses during exercise (ventilation, breathing pattern, heart rate, inspiratory capacity) under the different treatment conditions.

Assessment and procedures

Pulmonary function testing
Spirometry, lung volumes and diffusion capacity will be measured according to routine techniques.

Progressive maximal exercise test (Incremental shuttle walk test)
As originally described by Singh and colleagues[24], the incremental shuttle walk test will be performed in an enclosed corridor on a flat 10-m-long course. The course will be identified by two cones, each positioned 0.5 m from either end to allow patients to walk in circle and thereby avoid the need for abrupt changes in direction. Patients will walk at a predetermined rhythm, as dictated by an audio signal played from an audio recording. Walking speed will initially be set at 0.50 m/sec and will be increased by 0.17 m/sec every minute until the patient reaches maximal capacity. Since the effects of encouragement on walking performance have been demonstrated[25], no encouragement will be given to patients throughout the test. The final measure will be distance walked, expressed in meters.

3-min constant speed shuttle test
This test consists in one bout of three minutes of walking at the initial walking speed of 4.0 km/h. Thirty minutes after this first bout of walking, a second test will be performed at either a faster or slower walking speed (see Manual of procedures for standardization of pulmonary and exercise testing). The second walking speed will be determined by the ability to carry through the test at 4.0 km/h. If a patient cannot complete the first test, then the second speed will be stepped down. If a patient is able to carry though the first test, then the second walking speed will be raised. Patients will be asked to perform two tests at two different speeds in order to determine, amongst the different speeds, the highest speed that can be sustained for the entire 3 minutes while reaching a dyspnea score > 3 on the modified Borg scale. In doing so, our objective is to induce a level of dyspnea that is sufficiently high to be amenable to therapy. These speeds are selected based on our previous work[19] showing that these were sufficiently demanding to induce measurable levels of dyspnea and that most moderate to severe patients with COPD are able to complete the test for the desired duration[19,20]. Patients will be directed to follow the audio signals for the entire 3 minutes of the test or until they became symptom limited. They will be instructed to walk, jog or run around the two cones of the shuttle course, in a set-up identical to that of the ISWT, in the hospital or medical clinic hallway pacing their walk/jog/run in a continuous way as not to wait at the cones for the following audio signal. A device (McRoberts' MoveTest) will used during all the walk tests to confirm if the selected walk speed is respected.

Cardiac and ventilatory measures
During each exercise test, cardiac and ventilatory parameters will be measured using a commercially available portable exercise circuit (Oxycon Mobile). Dyspnea will be assessed using a 10-point modified Borg scale that will be assessed by the operator that will enter the course to ask the patient while they are in movement or positioned at one extremity of the course. During the maximal incremental shuttle walking test, inspiratory capacities and dyspnea will be measured at rest, at two-minute intervals and at the end of test. During the 3-min constant speed shuttle test, dyspnea will be assessed at rest, at minute 1, 2, 2.5 and 3. During this test, inspiratory capacities will be measured at rest and at the end of the test, immediately following the assessment of dyspnea.

Pharmacovigilance requirements

Safety data collection and reporting must be compliant with the local regulations of the country/countries where the study is being run

This section summarizes the procedures for the collection, management and reporting of individual cases of serious adverse events and should include the collection of any new information that might influence the evaluation of the benefit-risk balance of the product while the study is being conducted. Any Serious adverse event (SAE) exempt from this reporting process must be clearly identified in the study protocol with a scientific/medical justification e.g. SAEs due to disease progression, SAEs due to surgical procedure, pain in cancer patients, etc. Any SAE study protocol exemptions must be agreed with the respective country health authority as part of the protocol approval process. For studies where reporting is not required, this should be stated. Details on which data collected by the sponsor must be shared with Novartis, how this data is transferred to Novartis and the timelines for this transfer must be captured in the Third Party Study/Investigator Initiated Trial agreement. Additionally sharing of randomization data should be done as per Third Party Study/Investigator Initiated Trial agreement.

SAE Reconciliation

For integrated studies SAE reconciliation should be performed as defined in the Trial specific agreement including periodicity of reconciliation to avoid any missed SAEs from clinical and safety databases. Any deviation to the below text should be discussed with Novartis Drug Safety and Epidemiology.

Definition of an AE

Any untoward medical occurrence in a subject administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the investigational medicinal product.

Investigational Medicinal Product (IMP) includes the drug under evaluation and the comparator drug(s) if specified as part of the research objective, given at any time during the study. Medical conditions/diseases present before starting the drug of interest are only considered adverse events if they worsen after starting the drug of interest.

The occurrence of adverse events will be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All adverse events will be recorded in the study database including the following information:

1. The severity grade (mild, moderate, severe)
2. Its relationship to the drug(s) of interest (suspected/not suspected)
3. Its duration (start and end dates or if continuing at final exam)

4. Whether it constitutes a serious adverse event (SAE) A SAE is any untoward medical occurrence that at any dose:
   - Results in death,
   - Is life-threatening,
   - Requires inpatient hospitalization or prolongation of existing hospitalization,
   - Results in persistent or significant disability/incapacity,
   - Is a congenital anomaly/birth defect,
   - Is otherwise a significant medical event.

This includes any SAEs likely to arise from the trial indication or progression of underlying/concomitant illness(es) (e.g. progression of cancer in oncology trials), unless specified in the protocol as study specific exemptions.

Any SAE, irrespective of causality, occurring after the subject has provided informed consent and until four weeks after the subject has stopped study participation must be reported unless otherwise stated in the protocol. SAEs occurring after four weeks from ending study participation should only be reported if considered by the Investigator attributable to the exposure to the investigational drug(s) during the trial period. This includes the period in which the study protocol interferes with the standard medical treatment given to a subject, even if study treatment has not yet started (e.g. withdrawal of previous treatment during washout period, change in treatment to a fixed dose of concomitant medication).

Timelines
All serious adverse events (SAEs) from interventional clinical trials must be reported by the sites to Sponsor within 24 hours of occurrence of the SAE. The timelines for investigator initiated trials reporting to Novartis will be done as per Third Party Study/Investigator Initiated Trial Agreement.

Follow-up reports
SAEs will be followed until resolution or until it is judged to be permanent, and an assessment will be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the drug of interest, the interventions required to treat it, and the outcome.

The Sponsor shall support Novartis in the following-up of all SAEs so that complete information is available to maintain patient safety and also as part of any commitments by Novartis to any Health authority OR specific Health authority follow-up requests for the product under investigation.

Pregnancies
Any occurrences of a pregnancy in a patient (or a patients partner) during study participation will be collected. All pregnancies will be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Unsual lack of efficacy (LOE)
For drugs marketed in Canada, domestic reports of unusual failure in efficacy must be reported to Health Canada, by the sponsor of the trial. Lack of efficacy is defined as lack of anticipated clinical benefit or response with or without worsening. A copy should also be sent within 15 days of awareness to the local Novartis Drug Safety and Epidemiology Department at drug.safety@novartis.com. The original copy of the e-mail correspondence should be kept at the study site.

Analysis: Prospective determination of the initial walking speed during the 3-min CSST
The approach that we have adopted in this protocol and in previous studies involving the 3-min CSST to determine the initial walking speed to be used in patients is a pragmatic one; based on our experience, 4.0 km/hr is a walking speed that can be tolerated for 3 minutes in a majority of patients with moderate to severe COPD. However, in a proportion of patients, it is not the optimal walking speed, being either too fast or too slow in some patients. In this regard, it would be extremely useful to be able to predict, in a given patient, the optimal walking speed to be used during the CSST. Based on retrospective analysis of the studies we have conducted with the 3-min CSST[26,27], we are currently developing a promising predictive equation to determine the optimal walking speed. The equation is based on simple clinical characteristics such as age, sex, BMI, FEV1 and mMRC dyspnea score. We will use to data collected as a part of the current study to prospectively validate this equation.

Start date: Fall 2015
End date: Fall 2016
Study Report date: January 2017
Publication date: Submission June 2017

Note: The Study Report should include data on demographics, all efficacy endpoints, secondary endpoints, exploratory endpoints and safety events. Final Study Report to be sent to the Novartis Medical Responsible no later than 12 months after the last visit of the last patient.

Key-references:

1. O'Donnell DE, Fluge T, Gerken F, Hamilton A, Webb K, Aguilaniu B, Make B, Magnussen H. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. *Eur Respir J* 2004;23:832-840. Template Version 20 April 2014

2. O'Donnell DE, Voduc N, Fitzpatrick M, Webb KA. Effect of salmeterol on the ventilatory response to exercise in chronic obstructive pulmonary disease. *Eur Respir J* 2004;24:86-94.

3. Maltais F, Hamilton A, Marciniuck D, Hernandez P, Sciurba F, Richter K, Kesten S, O'Donnell DE. Improvements in symptom-limited exercise performance over eight hours with once-daily tiotropium in patients with COPD. *Chest* 2005;128:1168-1178.

4. Neder JA, Fuld JP, Overend T, Thirlwell J, Carter R, Stevenson R, Ward SA. Effects of formoterol on exercise tolerance in severely disabled patients with copd. *Respir Med* 2007;101:2056-2064.

5. Maltais F, Celli B, Casaburi R, Porszasz J, Jarreta D, Seoane B, Caracta C. Aclidinium bromide improves exercise endurance and lung hyperinflation in patients with moderate to severe COPD. *Respir Med* 2011;105:580-587.

6. O'Donnell DE, Casaburi R, Vincken W, Puente-Maestu L, Swales J, Lawrence D, Kramer B. Effect of indacaterol on exercise endurance and lung hyperinflation in copd. *Respir Med* 2011;105:1030-1036.

7. Beeh KM, Singh D, Di Scala L, Drollmann A. Once-daily NVA237 improves exercise tolerance from the first dose in patients with COPD: The GLOW3 trial. *Int J Chron Obstruct Pulmon Dis* 2012;7:503-513.

8. Combivent Inhalation Aerosol Study G. In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. *Chest* 1994;105:1411-1419.

9. Bateman ED, Ferguson GT, Barnes N, Gallagher N, Green Y, Henley M, Banerji D. Dual bronchodilation with qva149 versus single bronchodilator therapy: The SHINE study. *Eur Respir J* 2013;42:1484-1494.

10. Donohue JF, Maleki-Yazdi MR, Kilbride S, Mehta R, Kalberg C, Church A. Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. *Respir Med* 2013;107:1538-1546.

11. Wedzicha JA, Decramer M, Ficker JH, Niewoehner DE, Sandstrom T, Taylor AF, D'Andrea P, Arrasate C, Chen H, Banerji D. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (spark): A randomised, double-blind, parallel-group study. *Lancet Respir Med* 2013;1:199-209.

12. Celli B, Crater G, Kilbride S, Mehta R, Tabberer M, Kalberg CJ, Church A. Once-daily umeclidinium/vilanterol 125/25 mcg in COPD: A randomized, controlled study. *Chest* 2014;145:981-991.

13. Mahler DA, Decramer M, D'Urzo A, Worth H, White T, Alagappan VK, Chen H, Gallagher N, Kulich K, Banerji D. Dual bronchodilation with QVA149 reduces patient-reported dyspnoea in COPD: BLAZE study. *Eur Respir J* 2014;43:1599-1609.

14. Maltais F, Mahler DA, Pepin V, Nadreau E, Crater GD, Morris AN, Emmett AH, Ferro TJ. Effect of fluticasone propionate/salmeterol plus tiotropium versus tiotropium on walking endurance in COPD. *Eur Respir J* 2013;42:539-541. Template Version 20 April 2014

15. Beeh KM, Korn S, Beier J, Jadayel D, Henley M, D'Andrea P, Banerji D. Effect of qva149 on lung volumes and exercise tolerance in COPD patients: The BRIGHT study. *Respir Med* 2014;108:584-592.

16. Maltais F, Singh S, Donald AC, Crater G, Church A, Goh AH, Riley JH. Effects of a combination of umeclidinium/vilanterol on exercise endurance in patients with chronic obstructive pulmonary disease: Two randomized, double-blind clinical trials. *Ther Adv Respir Dis* 2014;8:169-181.
17. O'Donnell DE, Lam M, Webb KA. Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;160:542-549.

18. Brouillard C, Pepin V, Milot J, Lacasse Y, Maltais F. Endurance shuttle walking test: Responsiveness to salmeterol in COPD. *Eur Respir J* 2008;31:579-584.

19. Perrault H, Baril J, Henophy S, Rycroft A, Bourbeau J, Maltais F. Paced-walk and step tests to assess exertional dyspnea in COPD. *COPD* 2009;6:330-339.

20. Sava F, Perrault H, Brouillard C, Darauay C, Hamilton A, Bourbeau J, Maltais F. Detecting improvements in dyspnea in COPD using a three-minute constant rate shuttle walking protocol. *COPD* 2012;9:395-400.

21. O'Donnell DE, Sciurba F, Celli B, Mahler DA, Webb KA, Kalberg CJ, Knobil K. Effect of fluticasone propionate/salmeterol on lung hyperinflation and exercise endurance in COPD. *Chest* 2006;130:647-656.

22. Mahler DA, Waterman LA, Ward J, McCusker C, ZuWallack R, Baird JC. Validity and responsiveness of the self-administered computerized versions of the baseline and transition dyspnea indexes. *Chest* 2007;132:1283-1290.

23. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD assessment test. *Eur Respir J* 2009;34:648-654.

24. Singh SJ, Morgan MD, Scott S, Walters D, Hardman AE. Development of a shuttle walking test of disability in patients with chronic airways obstruction. *Thorax* 1992;47:1019-1024.

25. Guyatt GH, Pugsley S, Sullivan MJ, Thompson PJ, Berman L, Jones NL, Fallen EL, Taylor DW. Effect of encouragement on walking test performance. *Thorax* 1984;39:818-822.

26. Perrault H, Baril J, Henophy S, et al. Paced-walk and step tests to assess exertional dyspnea in copd. *COPD* 2009;6:330-339.

27. Sava F, Perrault H, Brouillard C, et al. Detecting improvements in dyspnea in copd using a three-minute constant rate shuttle walking protocol. *COPD* 2012;9:395-400.

François Maltais
May 30, 2016

To be completed for all Third Party Studies (TPS)/ Investigator-Initiated Trials (IITs) by the investigator Novartis supports medically and scientifically sound independent research initiated by external investigators and aimed at the advancement of scientific knowledge in therapeutic areas of interest for Novartis. Novartis evaluates unsolicited proposals from independent researchers or their institutions for support. By signing below you represent that the research proposal you are submitting was independently conceived by you and not solicited by any Novartis employee.

_____ _____

Investigator's Signature **Date**