Official Title: A Phase II, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Lebrikizumab in Patients with Chronic Obstructive Pulmonary Disease and a History of Exacerbations

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PROTOCOL

TITLE:	**A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF LEBRIKIZUMAB IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND A HISTORY OF EXACERBATIONS**
PROTOCOL NUMBER:	WB29804
VERSION NUMBER:	2
EUDRACT NUMBER:	2015-001122-42
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TEST PRODUCT:	Lebrikizumab (RO5490255)
MEDICAL MONITOR:	[redacted], *M.D., ScD.*
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 31 March 2015
DATE AMENDED:	Version 2: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	21-Dec-2015 19:18:30

CONFIDENTIAL

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PROTOCOL AMENDMENT, VERSION 2:
RATIONALE

Changes to Protocol WB29804, along with a rationale for each change, are summarized below.

INCLUSION AND EXCLUSION CRITERIA (Sections 4.1.1 and 4.1.2)

The protocol inclusion criteria have been amended to aid in patients with chronic obstructive pulmonary disease (COPD) recruitment.

The following changes have been introduced:

- Increasing the upper age limit to 80 years of age
- Allowing the inclusion of patients who have only received antibiotics for the treatment of exacerbations
- Increasing the timeframe allowed for a historical X-ray or CT scan from 3 months to 6 months
- Removal of the exclusion of BMI >38 kg/m^2
- Simplifying the exclusion language around infection and antibiotic use

PRIMARY ENDPOINT CHANGED TO 12 WEEKS FROM 24 WEEKS (Sections 6.4, 6.4.1, 6.4.2, 6.7, and 6.8)

Protocol WB29804, Version 1 had an interim analysis planned for when the total study population completed Week 12. Moving the primary endpoint of FEV1 change from 24 weeks to 12 weeks will allow a more robust use of the data post-interim analysis. The data at Week 12 is expected to be comparable to Week 24 as changes in lung function (FEV1) will be observed as early as Week 8.

PD BIOMARKERS (Section 6.7)

These samples are mandatory in Version 2 to allow for sufficient number of patient samples for meaningful data analysis at the end of the study. The sample collection timepoints at Screening and Weeks 1, 4, 8, and 28 have been removed to reduce patient burden.

Appendix 8: Childbearing Potential, Pregnancy Testing, and Contraception

The wording has been modified to comply with the current internal guidelines and template language.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 2:
SUMMARY OF CHANGES

GLOBAL CHANGES

The Medical Monitor has been changed from [redacted], M.D., M.S. to [redacted], M.D., ScD.

"Non-serious" has been removed from instances of "non-serious adverse events of special interest" throughout the protocol.

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 1.1: BACKGROUND ON COPD

COPD has been recognized as a progressive disease characterized by an accelerated rate of decline in FEV1 over time (GOLD 2015). COPD is a heterogeneous disorder comprising a number of different phenotypes, including airflow limitation and exacerbations. The extent of inflammation, fibrosis, and luminal exudates in small airways is correlated with the reduction in FEV_1 and FEV_1/forced vital capacity (FVC) ratio, and likely with the accelerated decline in FEV_1 (Celli et al. 2008). This peripheral airway obstruction progressively traps air during expiration resulting in hyperinflation. Gas exchange abnormalities result in hypoxemia and hypercapnia and have several mechanisms in COPD. In general, gas transfer for oxygen and carbon dioxide worsens as the disease progresses (GOLD 2015).

SECTION 1.3: STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

In patients with COPD and high blood eosinophil counts and/or periostin levels at baseline, the underlying disease biology may share similarities to Th2-driven asthma. A recent Phase IIa study with benralizumab, an anti-IL-5R monoclonal antibody, suggested *a beneficial effect*~~proof-of-concept with benefit~~ on FEV_1 and a trend towards a reduction in the rate of acute COPD exacerbations in patients with blood eosinophils $\geq$300 cells/μL (Brightling et al. 2014). Given the potential similarity in disease biology, lebrikizumab may also provide benefit in a COPD population. Therefore, this Phase II study aims to evaluate the safety, efficacy, and pharmacokinetics of lebrikizumab in patients with COPD, as well as the utility of baseline serum periostin and blood eosinophil levels in identifying patients who are most likely to receive clinical benefit.

SECTION 2.1: EFFICACY OBJECTIVES

The primary efficacy objective for this study is:

- To evaluate the efficacy of lebrikizumab compared with placebo in improving lung function, as measured by the absolute change in pre-bronchodilator FEV_1 in patients with COPD and a history of exacerbations *in the biomarker-high group (elevated*

- ~~To evaluate the efficacy of lebrikizumab using~~ serum periostin and blood eosinophils*) and biomarker-low group.* ~~as biomarkers that can identify patients with COPD who are most likely to receive benefit from lebrikizumab therapy~~

The secondary efficacy objective for this study is as follows:

- To evaluate *in the biomarker high and biomarker-low groups* the rate of moderate and severe COPD exacerbations, change in post-bronchodilator FEV_1, time to first exacerbation, and change in health-related quality of life and change in symptoms as measured by the Saint George's Respiratory Questionnaire for COPD patients (SGRQ-C), EXAcerbations of Chronic Pulmonary Disease Tool (EXACT), and Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI)

SECTION 2.3: PHARMACOKINETIC OBJECTIVES

The pharmacokinetic (PK) objective for this study is as follows:

- To evaluate serum lebrikizumab concentrations *and PK parameters* in patients with COPD and a history of exacerbations

SECTION 2.4: EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- *To evaluate the change in the six-minute walk test (6MWT) from baseline to Week 24*
- To evaluate IL-13–related and COPD–related PD biomarkers, changes in measures of lung function, ~~changes in measures of exercise tolerance,~~ and rescue medication use

SECTION 3.1: DESCRIPTION OF STUDY

Written informed consent for participation in the study must be obtained before performing any study-specific tests or evaluations. Patients then commence a screening period of approximately 14 days that includes a screening visit (Visit 1) as well as a final assessment of eligibility prior to randomization at Visit 2. During the screening period, patients will be assessed for adherence with their current COPD background therapy, their ability to use the equipment necessary for monthly clinic visits throughout the study, and the degree of dyspnea, and will be evaluated to determine if they meet all other eligibility criteria. ~~The screening period may be extended for selected reasons.~~

Patients may be eligible for rescreening up to two additional times*, with all inclusion and exclusion criteria being re-assessed.*

After screening has been completed, eligible patients will be randomized in a 1:1 ratio to receive double-blind treatment with subcutaneous (SC) lebrikizumab 125 mg or placebo, administered every 4 weeks. Randomization will be stratified by biomarker status (biomarker high [baseline blood eosinophil counts $\geq$300 cells/μL or periostin $\geq$50 ng/mL] or biomarker low [baseline blood eosinophil counts $<$300 cells/μL and periostin $<$50 ng/mL]), history of moderate/severe COPD exacerbations within the last 12 months

(1, >1 event), smoking status (current, former), geographical region*(American Continent, rest of world [ROW]),* and participation in the computed tomography (CT) scan substudy (yes, no).

The first dose of study drug *should* ~~will~~ be administered ~~on the same day~~ as *close to* randomization *as possible* (Visit 2 [Day 1]), and dosing will be repeated once every 4 weeks during a 24-week placebo-controlled period (for a total of 6 doses). Patients will continue on stable doses of their standard-of-care therapy that must include ICS therapy and a long-acting bronchodilator inhaler medication, in addition to receiving double-blind study drug, for *the duration of the study* ~~24 weeks~~.

Safety, efficacy, and patient-reported outcome (PRO) measures will be assessed throughout the placebo-controlled period as detailed in the schedule of assessments (see Appendix 1). The primary efficacy endpoint is the absolute change in pre-bronchodilator FEV_1 (liters) from baseline to Week *12* ~~24~~.

SECTION 3.2: END OF STUDY

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs. The LPLV is expected to occur ~~a maximum of~~ *approximately* 36 weeks after the last patient is randomized into the study. This timeframe includes a 24-week placebo-controlled period and a 12-week safety follow-up period.

SECTION 3.3.1: Rationale for Lebrikizumab Dose and Schedule

The selected Phase II dose *for COPD* is 125 mg given by SC injection every 4 weeks. The dosing frequency is supported by the half-life of lebrikizumab of approximately 25 days as well as the safety and efficacy data from Phase II asthma studies with the same dosing frequency.

In the Phase II asthma studies, lebrikizumab 250 mg, 125 mg, and 37.5 mg have demonstrated ~~efficacy~~ *effects* in reducing the rate of asthma exacerbations and improving FEV_1 in moderate-severe asthma patients. In the Phase II study ILR4646g, there was a trend for the 250-mg dose of lebrikizumab (the only dose evaluated) to reduce the rate of severe asthma exacerbations in periostin-high patients whose asthma was uncontrolled despite treatment with ICS therapy. In a Phase II dose-ranging study, Study ILR4660g, of lebrikizumab in patients not treated with ICS therapy, a similar magnitude of FEV_1 improvement and similar reduced risk for treatment failure was observed at the 125- and 250-mg dose levels. In the Phase IIb studies GB27862 and GB27864, the 250-mg dose did not provide incremental benefit above the treatment benefit seen with 125-mg on rate of asthma exacerbations or FEV_1 in periostin-high patients. While the 37.5 mg dose demonstrated ~~efficacy~~ *an effect* on rate of exacerbations, the confidence intervals were wide, and the 37.5-mg dose demonstrated lower benefit on mean placebo-corrected FEV_1 improvement. Based on these data, a dose of 125 mg is expected to demonstrate clinical efficacy in the ongoing Phase III asthma trials.

~~The underlying disease biology may be similar in biomarker-high patients with asthma and biomarker-high patients with COPD selected using the same biomarkers indicative of IL-13 driven inflammation in the lung (serum periostin and blood eosinophils). In addition, the IL-13 expression levels in induced sputum were shown to be similar between patients with asthma and patients with COPD (Grubek-Jaworska et al. 2012~~*There are reports of raised IL-13 (Lee et al. 2007) and periostin (Fingleton et al. 2014) in COPD. As with asthma, the findings are variable, although there is consensus that a subpopulation of patients with COPD appears to exhibit elevations of these and other markers of Th2 disease and to respond to ICS. The therapeutic response to ICS in these patients appears to be associated with reduction in periostin (Fingleton et al. 2014).*

The 125-mg dose, which ~~is anticipated~~ *has been shown* to be effective in patients with asthma, is expected to maintain sufficiently high drug levels to neutralize IL-13 in the lung of COPD patients, and has, therefore, been selected for this ~~proof-of-concept~~ study.

SECTION 3.3.4: Rationale for Biomarker Assessments

Biomarker-high patients will be defined as patients with baseline periostin ≥50 ng/mL or blood eosinophils ≥300 cells/μL, and patients with baseline periostin <50 ng/mL and blood eosinophils <300 cells/μL will be considered biomarker-low. *Other ranges might be explored at the end of the study.*

Blood samples will be collected at baseline and throughout the study to assess the relationship between periostin, blood eosinophils, and other IL-13/COPD–related biomarkers, including but not limited to *total* IgE, CCL-13, CCL-17, ~~and~~ CCL-18*, and fibrinogen* and changes in clinical status. If novel IL-13 or COPD-related biomarkers are identified, they may be measured from stored serum.

SECTION 3.4.1: Efficacy Outcome Measures

The primary efficacy endpoint for this study is as follows:

- Absolute change in pre-bronchodilator FEV_1 (liters) from baseline to Week *12*~~24~~

The secondary efficacy endpoints are as follows:

- *Absolute change in pre-bronchodilator FEV_1 (liters) from baseline to Week 24*

SECTION 3.4.4: Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- ~~Absolute change in pre-bronchodilator FEV_1 (liters) from baseline to Week 12~~

SECTION 4.1.1: Inclusion Criteria

Patients must meet the following criteria for study entry:

- Age 40*–80*~~75~~ years old at Visit 1
- ~~mMRC score ≥1 at Visit 1 or Visit 2~~

- Documented history of one or more acute COPD exacerbations that required treatment with systemic corticosteroids and/or *antibiotics or* hospitalization within 12 months prior to Visit 1
- Current *tobacco* smoker or former smoker *(having stopped smoking for at least 6 months prior to Visit 1)* with a ~~tobacco~~ history of *smoking* ≥10 pack-years *(20 cigarettes/day for 10 years). A former smoker may not have used inhaled tobacco products or inhaled marijuana within the past 3 months (e.g., cigarettes, cigars, electronic cigarettes, or pipe tobacco).*
- On ICS therapy for ≥6 months prior to Visit 1
- On an eligible bronchodilator medication (LABA, ~~or~~ LAMA, or both) for ≥6 months prior to Visit 1
- Chest X-ray or CT scan within *6* ~~3~~ months prior to Visit 1 or chest X-ray during the screening period (prior to Visit 2) that confirms the absence of clinically significant lung disease besides COPD
- For women who are not postmenopausal (≥12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined contraceptive methods that result in a failure rate of <1% per year for the duration of the study (during the placebo-controlled period and the safety follow-up period) *(see Appendix 8)*

SECTION 4.1.2: Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- ~~Infection that meets any of the following criteria:~~
- Any infection that resulted in hospital admission for ≥24 hours *and/*~~within 4 weeks prior to Visit 1~~ or ~~during screening Any infection that required~~ treatment with *oral,* IV, or IM antibiotics within 4 weeks prior to Visit 1 or during screening ~~Any active infection that required treatment with oral antibiotics within 2 weeks prior to Visit 1 or during screening~~
- ~~Body mass index >38 kg/m^2~~

SECTION 4.2: METHOD OF TREATMENT ASSIGNMENT AND BLINDING

…Patients *should*~~will~~ be randomized *as close as possible to*~~on~~ the ~~same~~ day that treatment is to be initiated (Visit 2 [Day 1]).

Randomization will be stratified by biomarker status (biomarker high [baseline blood eosinophil levels ≥300 cells/μL or periostin ≥50 ng/mL], biomarker low [baseline blood eosinophil levels <300 cells/μL and periostin <50 ng/mL)], history of moderate/severe COPD exacerbations within the last 12 months (1, >1 event), smoking status (current, former), geographical region *(American Continent, ROW),* and participation in the CT substudy (yes, no). A permuted block randomization will be used to obtain an approximately 1:1 ratio between the two treatment arms within each stratum. At each dosing visit during the placebo-controlled treatment period, study treatment kits will be assigned via the IxRS. The placebo and active kits are filled and packaged to look

identical. Patients and all study site personnel will be blinded to treatment assignment until all patients have either completed the study through the safety follow-up period or discontinued early from the study, the database is locked, and the study analyses are final. The Sponsor and its agents will be blinded to treatment assignment ~~throughout the 24-week placebo-controlled period~~ *until all subjects have either completed their Week 12 visit or discontinued from the placebo-controlled period early*, with the exception of the following agents who will not be blinded to treatment assignment during the study: IxRS service provider, ~~external independent statistical coordinating center responsible for verifying patient randomization and study drug kit assignments,~~ bioanalytical laboratory personnel, and Internal Monitoring Committee (IMC) members. Treatment assignment will be unblinded ~~to the personnel analyzing data from the placebo-controlled period~~ *the Sponsor*~~at the time of optional interim~~ *for the primary* analysis.~~and when all data through Week 24 are in the database and the data have been cleaned and verified (see Section 6 for details on the analysis).~~

The primary analysis will be performed when all subjects have completed their Week 12 visit or discontinued from the placebo-controlled period early and after all data are in the database and the data have been cleaned and verified. To minimize biases, investigators, patients as well as the study team members other than those mentioned above will remain blinded at the patient level until the final database lock.

Study completion is defined as all subjects having completed safety follow-up through Week 36 or discontinued from the study early. Patients and all study site personnel will be blinded to periostin and other PD biomarker levels until study completion, except as described below. Sponsor study team members who have direct contact with study sites will remain blinded to individual periostin and blood eosinophil levels, but team members who do not interact with study sites may review individual pretreatment periostin and blood eosinophil levels for assessment of baseline study information and ongoing review of data quality. The Sponsor will remain blinded to individual post-treatment periostin and other post-treatment PD biomarker levels until *the primary analysis* ~~completion of the placebo-controlled period~~. Eosinophil counts during screening will be reviewed by the sites as part of routine laboratory data review. Patients, all study site personnel, and the Sponsor will be blinded to eosinophil counts post-randomization except for clinically significant elevations in eosinophil counts which will be reported to sites and may be reviewed by the Sponsor as part of routine safety monitoring. If clinically indicated, sites may obtain a white blood cell count and differential (including eosinophil count) at their local laboratory.

SECTION 4.5.1.7: Tobacco Cessation for Current Smokers

At Visit 1, patients who are current smokers will receive tobacco cessation counseling. *Current smokers are defined as those with history of cigarette smoking of ≥10 pack-years. Former smokers are defined as those who meet the definition of current smoker but have stopped smoking at least 6 months prior Visit 1.*

SECTION 4.5.1.10: Patient-Reported Outcomes
Modified Medical Research Council Dyspnea Scale

The mMRC scale assesses dyspnea (Bestall et al. 1999). Patients rate how much their breathlessness impacts their mobility. The mMRC is a five-item scale. Zero represents the least impairment due to dyspnea and four indicates greatest impairment due to dyspnea. There is no recall period for the mMRC. The mMRC is administered at the site on paper. The mMRC is completed at Visit 1 and Visit 2 *and* ~~to determine whether the patient is eligible for this study. The mMRC is~~ also completed throughout the treatment *and follow-up* period as a component of the BODE index, as specified in the schedule of assessments (see Appendix 1). A copy of the scale is available in Appendix 5.

SECTION 4.5.1.13: Chest X-Rays

A chest X-ray must be performed during screening (between Visit 1 and Visit 2) unless a chest X-ray or CT scan has been ~~obtained~~ *performed* within *6* ~~3~~ months prior to Visit 1 and *the scan or radiologist report* is available for review by the investigator. The X-ray may be performed locally but *the X-ray or radiologist report* must be reviewed by the investigator prior to randomization at Visit 2. If a chest X-ray or CT scan is not available in the *6* ~~3~~ months preceding Visit 1 or a chest X-ray cannot be completed during screening, the patient will not be eligible for the study.

SECTION 4.5.1.16: Laboratory and Biomarker Samples

Samples for the following laboratory tests will be sent to one or several central laboratories for analysis:

- ~~Serum theophylline levels (patients taking theophylline only)~~

Samples for the following laboratory tests will be sent to the Sponsor or a designee for analysis:

- *Plasma for IL-13- and COPD-related biomarkers including but not limited to plasma PD samples for research purposes, including fibrinogen*

SECTION 4.5.1.18: Optional Samples for Roche Clinical Repository Sample Collection

The following samples will be collected for research on dynamic (non-inherited) biomarkers:

- ~~Plasma PD samples for research purposes, including, but not limited to, research on biomarkers related to IL-13, COPD, COPD-related diseases, or other respiratory diseases~~

SECTION 4.5.2.1: Screening and Pretreatment Assessments

Patients may be eligible for rescreening for selected reasons up to two additional times*, with all inclusion and exclusion criteria being re-assessed.*

A chest X-ray must be performed during screening unless a chest X-ray or CT scan has been ~~obtained~~*performed* within *6*~~3~~ months prior to Visit 1 and *the scan or radiologist report* is available for review by the investigator. The X-ray may be performed locally but *the scan or radiologist report* must be reviewed by the investigator prior to randomization at Visit 2. If a chest X-ray (or CT scan) is not available in the *6*~~3~~ months preceding Visit 1 and cannot be completed during screening, the patient will not be eligible for the study.

Patients not adherent with their background COPD medications from Visits 1 to 2, as evidenced by *<* 70% adherence during the screening period, will not be eligible for the study. However, the screening period may be extended by 1 week for additional adherence monitoring in the case of device malfunction or extenuating patient circumstances. *In such cases, the Sponsor or designee should be contacted to review the case prior to extending the screening period. If the screening period is extended* ~~When this occurs~~, the adherence calculation will be based on the number of days the patient was adherent to baseline therapy when the device was used and functioning properly.

SECTION 4.5.2.2: Assessments during Treatment

The 24-week placebo-controlled period begins *after* ~~at the~~ randomization *and* ~~visit (Visit 2) when the patient receives the~~ first dose of study drug*, once all study procedures and assessments have been completed*. Patients who complete study drug dosing visits during the 24-week placebo-controlled period will enter the safety follow-up period.

SECTION 5.1: SAFETY PLAN

Lebrikizumab is not an approved drug and is currently in clinical development *also* for asthma, atopic dermatitis, and idiopathic pulmonary fibrosis. Thus, the entire safety profile of lebrikizumab is not fully characterized at this time.

SECTION 5.1.1: Internal Monitoring Committee

The IMC will consist of Sponsor representatives from the following functions: Clinical Science, Drug Safety, *and* Biostatistics~~, and Statistical Programming and Analysis (SPA)~~. The IMC members will be external to the Sponsor's Study Management Team, except for the Biostatistics ~~and SPA~~ representative~~s~~.

SECTION 5.1.2.3: Infections

In addition, patients *with any* ~~will be excluded from study participation if they experience an episode of~~ infection *that results in* ~~requiring any of the following:~~ hospitalization *and/* ~~for ≥24 hours within 4 weeks prior to Visit 1, treatment with IV antibiotics within 4 weeks prior to Visit 1,~~ or treatment with oral*, IV, or IM* antibiotics ~~for an active infection~~ within *4*~~2~~ weeks prior to ~~Visit 1. Patients with an infection requiring any of the above treatments during~~ screening *or Visit 1* will ~~also~~ be excluded.

SECTION 5.3.5.1: *Injection-Site Reactions*

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug injection should be captured as a diagnosis (e.g., "injection-site reaction" or "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Injection Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Injection Reaction eCRF.

SECTION 5.3.5.5: Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is clinically significant in the investigator's judgment

  ~~Note: For oncology trials, certain abnormal values may not qualify as adverse events.~~

SECTION 5.3.5.8: Deaths

If the death is attributed to progression of COPD, then "COPD progression" should be recorded on the Adverse Event eCRF.

SECTION 5.3.5.11: Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization *(i.e., in-patient admission to a hospital) or prolonged*~~or prolongs~~ hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are <u>not</u> considered to be ~~a serious~~ adverse events:

- *Hospitalization for respite care*
- *Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)*
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The patient has not *experienced*~~suffered~~ an adverse event

The following hospitalization scenario is not considered to be a serious adverse event but should be reported as an adverse event instead:

- *Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours*

SECTION 5.4.1: Emergency Medical Contacts
Medical Monitor Contact Information

Medical Monitor: [redacted], *M.D., ScD.* [redacted], ~~M.D., M.S~~.
(primary)

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

SECTION 5.4.3.1: Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within ~~16~~*18* weeks after the last dose of study drug.…

SECTION 6: STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The primary and secondary efficacy analyses will be based on a modified intent-to-treat (mITT) approach. *The definition of mITT is* ~~A~~*a*ll patients randomized who received at least one dose of study drug will be included in the analysis, with patients grouped according to the treatment assigned at randomization.

The primary analysis will be performed after all patients have either completed the Week 12 visit or discontinued from the placebo-controlled period prematurely. The *final* analysis of data ~~from the 24-week placebo-controlled period~~ will be performed when all patients have either completed the Week ~~24~~ *36* visit or discontinued from the placebo-controlled period prematurely, and all data from the placebo-controlled period are in the database and have been cleaned and verified.

…All treatment group comparisons will be made within each of the biomarker-high (baseline blood eosinophils $\geq$300 cells/μL *or* baseline serum periostin $\geq$50 ng/mL) and biomarker-low (baseline blood eosinophils $<$300 cells/μL *and* baseline serum periostin $<$50 ng/mL) subgroups. *Other ranges might be explored.*

SECTION 6.1: DETERMINATION OF SAMPLE SIZE

The purpose of this study is to evaluate the efficacy of lebrikizumab compared with placebo in improving lung function, as measured by the change from baseline of pre-bronchodilator FEV_1 in biomarker-high COPD patients. ~~Point and interval estimates of the change from baseline of pre-bronchodilator FEV_1 within each treatment group/biomarker group combination as well as of the difference in change from baseline of pre-bronchodilator FEV_1 between treatment groups within each biomarker subgroup will be presented.~~

The study will enroll approximately 300 patients. Patients will be randomized in a 1:1 ratio to receive treatment with either lebrikizumab 125 mg or placebo every 4 weeks, in addition to standard-of-care COPD medications. The sample size of 150 patients per arm provides at least 80% power to detect a 77 mL (approximately 5.7 percent change from baseline [Dransfield et al. 2014]) difference in pre-bronchodilator FEV_1 change from

baseline at Week*s 12 and* 24 between treatment groups among patients within the biomarker-high subgroup (75 biomarker-high patients in the lebrikizumab arm compared with 75 biomarker-high patients in the placebo arm) under the following assumptions:

- The absolute change from baseline at Week *12*~~24~~ in pre-bronchodilator FEV_1 is normally distributed with a standard deviation of 210 mL
- Drop-out rate at Week *12*~~24~~ is 10%, leading to a 10% loss of information

SECTION 6.3: SUMMARIES OF TREATEMNT GROUP COMPARABILITY

Demographic and baseline characteristics, such as age, sex, race/ethnicity, blood eosinophil level, serum periostin level, smoking status, history of COPD exacerbations within the last 12 months, pulmonary function, health status (as measured by the SGRQ-C), comorbid illness, baseline COPD medications (double vs. triple therapy), bronchodilator reversibility (present, absent), geographical region *(American Continent, ROW),* and participation in the CT substudy (yes, no) will be summarized for all randomized patients by treatment arm and biomarker subgroup using descriptive statistics (e.g., mean, standard deviation, minimum and maximum). Exposure to study drug (number of study drug treatments and duration of treatment) will be summarized by treatment arm, biomarker subgroup, and study period.

SECTION 6.4: EFFICACY ANALYSES

~~Hypothesis testing for t~~*T*he primary efficacy endpoint and each secondary efficacy endpoint will each be performed separately within a*n appropriate* ~~single generalized linear~~ *regression* model (one per endpoint) *as* specified below *in Sections 6.4.1 and Section 6.4.2*. All models *(except for time to first severe or moderate COPD exacerbation)* will include as covariates: treatment group, biomarker subgroup (as defined in Section 6), treatment group by biomarker subgroup interaction, baseline history of COPD exacerbations within the last 12 months (1, $>$1 event), baseline COPD medications (double vs triple therapy), smoking status (current, former), bronchodilator reversibility (present, absent), and geographical region *(American Continent, ROW)* as covariates. The study is sized to obtain point estimates and confidence intervals for treatment group differences *within* the biomarker-high subgroup, but not to detect treatment efficacy differences *between* biomarker-high and biomarker-low subgroups (test of biomarker subgroup by treatment group interaction effect).

All continuous endpoints measured at multiple visits will be analyzed using a mixed-~~-~~effect model repeated measurement (MMRM) model. All ~~specified mixed effect model repeated measurement (MMRM)~~ *such* models will in addition to the above covariates include visit, visit by treatment group interaction, visit by biomarker subgroup interaction, biomarker subgroup by treatment group interaction, treatment group by visit interaction, and three-way visit by biomarker subgroup by treatment group interaction as covariates. Therefore, missing data will be handled by the model under the missing-at-random assumption without need for imputation for early discontinuation.

The primary and secondary objectives in this~~e~~ study will be assessed in the biomarker-high population. *Models will include both biomarker-high and biomarker-low groups. Treatment effect estimates in both biomarker groups will be provided.*

Testing of the effect of lebrikizumab compared with placebo on a given endpoint within both biomarker-high and biomarker-low subgroups will be performed via ~~the t-test~~*a Wald* at the two-sided $\alpha = 0.20$ level of the between-group least squares mean (LSM) differences with the LSMESTIMATE statement in SAS. Two tests for each endpoint (one treatment comparison per biomarker subgroup) will be performed and p-values reported with no adjustment for multiplicity. Point and interval estimates of LSMs within each treatment/biomarker subgroup combination will be presented.

~~In addition to the analyses described in Section 6.4.1 and Section 6.4.2, the following analyses will be performed for the primary efficacy endpoint and key secondary efficacy endpoints. Details of these analyses will be documented in the Sponsor's trial master file prior to database lock.~~

- ~~Sensitivity analyses to evaluate the robustness of results to the analysis methods (e.g., robustness to parametric model assumptions, time-at-risk definition, handling of early treatment and/or study discontinuation, and the analysis population)~~
- ~~Sensitivity analysis to definition of biomarker-high subgroup including choice of biomarker(s) and associated cut-points~~

SECTION 6.4.1: Primary Efficacy Endpoint

The primary efficacy endpoint for this study is the absolute change in pre-bronchodilator FEV_1 (volume) from baseline to Week *12*~~24~~. The baseline pre-bronchodilator FEV_1 measurement is defined as the last spirometry measurement prior to or on the day of randomization. The primary endpoint will be analyzed using a MMRM model as specified in Section 6.4 *and assessments after Week 12 will be excluded from the MMRM model.* Baseline pre-bronchodilator FEV_1 will be included as an additional covariate. *Missing data will be handled by the model under the missing-at-random assumption without need for imputation for early discontinuation.* The treatment effect will be tested within each biomarker subgroup according to the procedure specified in Section 6.4. *Point and interval estimates of the change from baseline of pre-bronchodilator FEV1 within each treatment group/biomarker group combination as well as of the difference in change from baseline of pre-bronchodilator FEV1 between treatment groups within each biomarker subgroup will be presented. A sensitivity analysis with respect to protocol adherence will be performed by excluding data collected more than 6 weeks after last study drug administration.*

The assessment optimal cutoff for the biomarker-high group will be explored.

SECTION 6.4.2: Secondary Efficacy Endpoints

Rate of Moderate or Severe COPD Exacerbations

Using exacerbations observed from randomization to at most 172 days post-randomization (including data collected during safety follow-up in the case of early drug discontinuation), the within-biomarker subgroup covariate-adjusted exacerbation rates (LSMs) of each treatment group will be estimated using a ~~negative-binomial generalized linear~~*Poisson* model *with overdispersion. Missing data will be handled by the model under the missing at random assumption, without imputation for early study discontinuation.* In addition to the covariates specified in Section 6.4, the model will also include a log-transformed years-at-risk as an offset variable, without imputation for early discontinuation. *If for any baseline covariate level there are no COPD exacerbations observed in the analysis population resulting in non-convergence of the model fitting algorithm, that covariate will be dropped from the analysis.* The treatment effect will be tested within each biomarker subgroup according to the procedure specified in Section 6.4. *A sensitivity analysis with respect to early treatment discontinuation will be performed by excluding data collected more than 6 weeks after last study drug administration. Sensitivity of results to parametric model assumptions will be assessed by fitting a negative-binomial regression model.*

The assessment optimal cutoff for the biomarker-high group will be explored.

Absolute Change in Pre-Bronchodilator FEV_1

The same procedure outlined for the primary endpoint in Section 6.4.1 will be followed to analyze the change from baseline to Week 24 in pre-bronchodilator FEV_1.

Time to First Moderate or Severe COPD Exacerbation

The covariate-adjusted hazard ratios of treatment groups within biomarker subgroups will be tested using a Cox proportional hazard model ~~with~~ *stratified by* covariates specified in Section 6.4*: biomarker group, baseline history of COPD exacerbations within the last 12 months (1, >1 event), baseline COPD medications (double vs. triple therapy), smoking status (current, former), bronchodilator reversibility (present, absent), and geographical region (American Continent, ROW). Biomarker by treatment interaction effect will be included as covariates.* Patients who do not experience a protocol-defined exacerbation will be censored at the date of their Week 24 visit or date of early discontinuation, whichever occurs first. The treatment effect will be tested within each biomarker subgroup according to the procedure specified in Section 6.4.

SECTION 6.7: EXPLORATORY ANALYSES

~~Exploratory analyses of exploratory efficacy endpoint listed in Section 3.4.4 will follow the procedures outlined in Section 6.4. Analyses will be performed to explore the appropriateness of the eosinophil and periostin cut-points in defining the biomarker subgroup with respect to the primary and key secondary endpoints.~~

The following exploratory endpoints will be summarized using descriptive statistics by treatment group.

- *Absolute change in pre-bronchodilator FEV_1 (liters) from baseline to Week 4*
- *Change in the 6MWT distance from baseline to Week 24*
- *Change from baseline in blood eosinophils, serum periostin, IgE, CCL-13, CCL-17, and CCL-18 will be summarized by descriptive statistics*
- *Change in the body mass index, airflow obstruction, dyspnea, and exercise capacity (BODE) index from baseline to Week 24*
- *Change in COPD rescue medication use from baseline to Week 24*

Other PD biomarkers listed in Section 3.4.4 will also be explored. ~~Details of exploratory analyses will be documented in the Sponsor's trial master file prior to database lock.~~

SECTION 6.8: *INTERIM ANALYSES*

The interim safety analyses will be performed periodically and reviewed by the IMC.

~~Given the hypothesis-generating nature of this study, t~~*T*he Sponsor may choose to conduct up to two interim efficacy analyses. The decision to conduct an optional interim efficacy analysis and the timing of the interim efficacy analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim efficacy analysis. The interim efficacy analysis will be performed and interpreted by members of the Sponsor study team and appropriate senior management personnel who will be unblinded at the treatment group level. Access to treatment assignment information will follow the Sponsor's standard procedures.

SECTION 9.4: ADMINISTRATIVE STRUCTURE

~~An IMC will be used in this study to provide oversight of safety (see Section 5.1.1).~~

FIGURE 1: Study Schema

Figure 1 has been revised to reflect changes to the protocol.

TABLE 3: Sources of Statistical Assumptions used in Determining Power in Analysis of FEV_1 *at 24 Weeks*

Table 3 title has been updated.

APPENDIX 1: Schedule of Assessments

The schedule of assessments has been revised to reflect the changes to the protocol.

APPENDIX 8: Childbearing Potential, Pregnancy Testing, and Contraception

Appendix 8 has been revised to reflect changes to the protocol.

SAMPLE INFORMED CONSENT FORM

The sample Informed Consent Form has been revised to reflect the changes to the protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF LEBRIKIZUMAB IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND A HISTORY OF EXACERBATIONS**
PROTOCOL NUMBER:	WB29804
VERSION NUMBER:	2
EUDRACT NUMBER:	2015-001122-42
IND NUMBER:	125,626
TEST PRODUCT:	Lebrikizumab (RO5490255)
MEDICAL MONITOR:	[redacted], *M.D., ScD.*
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

Please retain the signed original of this form for your study files.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFICACY AND SAFETY OF LEBRIKIZUMAB IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND A HISTORY OF EXACERBATIONS**
PROTOCOL NUMBER:	WB29804
VERSION NUMBER:	2
EUDRACT NUMBER:	2015-001122-42
IND NUMBER:	125,626
TEST PRODUCT:	Lebrikizumab (RO5490255)
PHASE:	II
INDICATION:	Chronic obstructive pulmonary disease (COPD)
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Efficacy Objectives

The primary efficacy objective for this study is:

- To evaluate the efficacy of lebrikizumab compared with placebo in improving lung function, as measured by the absolute change in pre-bronchodilator FEV_1 in patients with COPD and a history of exacerbations *in the biomarker-high group (elevated* serum periostin and blood eosinophils*) and biomarker-low group.*

The secondary efficacy objective for this study is as follows:

- To evaluate *in the biomarker high and biomarker-low groups* the rate of moderate and severe COPD exacerbations, change in post-bronchodilator FEV_1, time to first exacerbation, and change in health-related quality of life and change in symptoms as measured by the Saint George's Respiratory Questionnaire for COPD patients (SGRQ-C), EXAcerbations of Chronic Pulmonary Disease Tool (EXACT), and Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI)

Safety Objectives

The safety objective for this study is as follows:

- To evaluate the safety of lebrikizumab compared with placebo in patients with COPD and a history of exacerbations, focusing on the nature, frequency, and severity of serious and non-serious adverse events

Pharmacokinetic Objectives

The pharmacokinetic (PK) objective for this study is as follows:

- To evaluate serum lebrikizumab concentrations *and PK parameters* in patients with COPD and a history of exacerbations

Exploratory Objectives

The exploratory objectives for this study are as follows:

- *To evaluate the change in the six-minute walk test (6MWT) from baseline to Week 24*

- To evaluate IL-13–related and COPD–related PD biomarkers, changes in measures of lung function, and rescue medication use

Study Design

Description of Study

This is a Phase II, randomized, multicenter, double-blind, placebo-controlled, parallel-group clinical trial of lebrikizumab in patients with COPD and a history of exacerbations who are treated with ICS and at least one long-acting bronchodilator inhaler medication (LABA or LAMA). Patients receiving additional background COPD medications are permitted to enter the study. This study will also assess baseline levels of serum periostin and baseline blood eosinophil counts as predictive biomarkers for identifying patients who may achieve clinically meaningful efficacy. Patients will be considered biomarker-high if the baseline serum periostin is $\geq$50 ng/mL or baseline blood eosinophil count is $\geq$300 cells/μL. The study consists of a screening period, a placebo-controlled period, and a safety follow-up period.

Written informed consent for participation in the study must be obtained before performing any study-specific tests or evaluations. Patients then commence a screening period of approximately 14 days that includes a screening visit (Visit 1) as well as a final assessment of eligibility prior to randomization at Visit 2. During the screening period, patients will be assessed for adherence with their current COPD background therapy, their ability to use the equipment necessary for monthly clinic visits throughout the study, and the degree of dyspnea, and will be evaluated to determine if they meet all other eligibility criteria.

Patients may be eligible for rescreening up to two additional times, with all inclusion and exclusion criteria being re-assessed.

After screening has been completed, eligible patients will be randomized in a 1:1 ratio to receive double-blind treatment with subcutaneous (SC) lebrikizumab 125 mg or placebo, administered every 4 weeks. Randomization will be stratified by biomarker status (biomarker high [baseline blood eosinophil counts $\geq$300 cells/μL or periostin $\geq$50 ng/mL] or biomarker low [baseline blood eosinophil counts $<$300 cells/μL and periostin $<$50 ng/mL]), history of moderate/severe COPD exacerbations within the last 12 months (1, $>$1 event), smoking status (current, former), geographical region(American Continent, rest of world [ROW]), and participation in the computed tomography (CT) scan substudy (yes, no).

The first dose of study drug *should* be administered as *close to* randomization *as possible* (Visit 2 [Day 1]), and dosing will be repeated once every 4 weeks during a 24-week placebo-controlled period (for a total of 6 doses). Patients will continue on stable doses of their standard-of-care therapy that must include ICS therapy and a long-acting bronchodilator inhaler medication, in addition to receiving double-blind study drug, for *the duration of the study*.

Safety, efficacy, and patient-reported outcome (PRO) measures will be assessed throughout the placebo-controlled period as detailed in the schedule of assessments (see protocol). The primary efficacy endpoint is the absolute change in pre-bronchodilator FEV_1 (liters) from baseline to Week *12*.

After the last dose of study drug in the placebo-controlled period, all patients will be followed for safety for 16 weeks (approximately 4 half-lives of lebrikizumab). This includes the 4 weeks after the final dose during the placebo-controlled period and a 12-week safety follow-up period. The safety follow-up period is detailed in the schedule of assessments.

All patients who discontinue study drug early in the placebo-controlled period will be asked to continue study assessments in the placebo-controlled period and then complete the safety follow-up period. Patients who are unwilling or unable to continue with assessments in the placebo-controlled period will complete a dosing termination (DT) visit and then enter safety follow-up.

Total participation in the study starting from randomization at Visit 2 (Day 1), including the 24-week placebo-controlled period and 12-week safety follow-up period, may be as long as 36 weeks.

Number of Patients

Approximately 70 sites will participate to enroll a total of approximately 300 patients.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Able and willing to provide written informed consent and to comply with the study protocol
- Age 40–*80* years old at Visit 1
- Able and willing to use the electronic device for patient-reported data collection
- Documented history of COPD diagnosis for ≥ 12 months prior to Visit 1
- Post-bronchodilator $FEV_1/FVC < 0.70$ at Visit 1 or Visit 2
- Post-bronchodilator $FEV_1 < 80\%$ predicted at Visit 1 or Visit 2
- Documented history of one or more acute COPD exacerbations that required treatment with systemic corticosteroids and/or *antibiotics or* hospitalization within 12 months prior to Visit 1
- Current *tobacco* smoker or former smoker *(having stopped smoking for at least 6 months prior to Visit 1)* with a history of *smoking* ≥ 10 pack-years *(20 cigarettes/day for 10 years). A former smoker may not have used inhaled tobacco products or inhaled marijuana within the past 3 months (e.g., cigarettes, cigars, electronic cigarettes, or pipe tobacco).*
- On ICS therapy for ≥ 6 months prior to Visit 1
- On an eligible bronchodilator medication (LABA, LAMA, or both) for ≥ 6 months prior to Visit 1
- Chest X-ray or CT scan within *6* months prior to Visit 1 or chest X-ray during the screening period (prior to Visit 2) that confirms the absence of clinically significant lung disease besides COPD
- Demonstrated adherence with background COPD inhaler medication during the screening period. Adherence is defined as patients responding affirmatively that they have taken their inhaler therapy ≥ 70% of days during the screening period (Visits 1–2), as recorded in their eDiary
- For women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined contraceptive methods that result in a failure rate of < 1% per year for the duration of the study (during the placebo-controlled period and the safety follow-up period)

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the lebrikizumab injection
- History of clinically significant pulmonary disease other than COPD
- Diagnosis of alpha-1-antitrypsin deficiency
- Lung volume reduction surgery or procedure within 12 months prior to Visit 1
- Supplemental oxygen requirement > 2 L/min at rest or with exertion
- Current diagnosis of asthma
- Patients participating in, or scheduled for, an intensive COPD rehabilitation program (patients who are in the maintenance phase of a rehabilitation program are eligible)
- Maintenance oral corticosteroid therapy, defined as daily or alternate-day oral corticosteroid maintenance therapy, within 3 months prior to Visit 1
- Treatment with systemic (oral, intravenous [IV], or intramuscular [IM]) corticosteroids within 4 weeks prior to Visit 1 or during the screening period for any reason, including an acute exacerbation event

- Unstable ischemic heart disease, arrhythmia, cardiomyopathy, or other relevant cardiovascular disorder that, in the opinion of the investigator, may put the patient at risk or negatively affect the study outcome
- Any infection that resulted in hospital admission for $\geq$24 hours *and/*or treatment with *oral,* IV*,* or IM antibiotics within 4 weeks prior to Visit 1 or during screening
- Upper or lower respiratory tract infection within 4 weeks prior to Visit 1 or during screening
- Active parasitic infection or *Listeria monocytogenes* infection within 6 months prior to Visit 1 or during screening
- Active tuberculosis requiring treatment within 12 months prior to Visit 1. Patients who have completed treatment for tuberculosis at least 12 months prior to Visit 1 and have no evidence of recurrent disease are permitted.
- Known immunodeficiency, including but not limited to HIV infection
- Evidence of acute or chronic hepatitis or known liver cirrhosis
- AST, ALT, or total bilirubin elevation $\geq 2.0 \times$ the upper limit of normal (ULN) during screening
- Clinically significant abnormality on screening ECG or laboratory tests (hematology, serum chemistry, and urinalysis) that, in the opinion of the investigator, may pose an additional risk in administering study drug to the patient
- Known current malignancy or current evaluation for a potential malignancy
- Other clinically significant medical disease that is uncontrolled despite treatment, that is likely, in the opinion of the investigator, to impact the patient's ability to participate in the study or impact the study efficacy or safety assessments
- History of alcohol or drug abuse that would impair or risk the patient's full participation in the study, in the opinion of the investigator
- Past and/or current use of any anti–IL-13 or anti–IL-4/IL-13 therapy, including lebrikizumab. Patients participating in a clinical trial that has not been unblinded should be assumed to have received the active drug.
- Treatment with an immunomodulatory or immunosuppressive monoclonal antibody (other than an anti–IL-13 or anti–IL-4/IL-13 therapy) within 6 months or 5 drug half-lives prior to Visit 1 (whichever is longer) or during screening. Patients participating in a clinical trial that has not been unblinded should be assumed to have received the active drug.
- Use of an immunomodulatory or immunosuppressive therapy (other than a monoclonal antibody or corticosteroids [see separate exclusion]) within 3 months or 5 drug half-lives prior to Visit 1 (whichever is longer) or during screening
- Use of other investigational therapy not described above within 4 weeks or 5 drug half-lives prior to Visit 1 (whichever is longer) or during screening. Patients participating in a clinical trial that has not been unblinded should be assumed to have received the active drug.
- Receipt of a live attenuated vaccine within 4 weeks prior to Visit 1 or during screening
- Pregnant or lactating
- Body weight $<$40 kg

Length of Study

Total participation in the study starting from randomization at Visit 2 (Day 1), including the 24 week placebo-controlled period and 12-week safety follow-up period, may be as long as 36 weeks.

End of Study

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs. The LPLV is expected to occur *approximately* 36 weeks after the last patient is randomized into the study. This timeframe includes a 24-week placebo-controlled period and a 12-week safety follow-up period.

Outcome Measures

Efficacy Outcome Measures

Each efficacy endpoint will be analyzed separately in biomarker-high and biomarker-low patients.

The primary efficacy endpoint for this study is as follows:

- Absolute change in pre-bronchodilator FEV_1 (liters) from baseline to Week *12*

The secondary efficacy endpoints are as follows:

- Rate of moderate/severe COPD exacerbations during the 24-week placebo-controlled period

  A moderate COPD exacerbation is defined as new or increased COPD symptoms (e.g., dyspnea, sputum volume, and sputum purulence) for at least 2 consecutive days that lead to treatment with systemic corticosteroids and/or antibiotics

  A severe COPD exacerbation is defined as new or increased COPD symptoms (e.g., dyspnea, sputum volume, and sputum purulence) for at least 2 consecutive days that lead to hospitalization

- Absolute change in post-bronchodilator FEV_1 (liters) from baseline to Week 24
- *Absolute change in pre-bronchodilator FEV_1 (liters) from baseline to Week 24*
- Time to first COPD exacerbation during the 24-week placebo-controlled period
- Change in health-related quality of life, as assessed by the overall score of the SGRQ-C, from baseline to Week 24
- Change in COPD symptoms as measured by the overall score on the EXACT from baseline to Week 24
- Change in cough and sputum as measured by the cough and sputum domain of the EXACT from baseline to Week 24
- Change in dyspnea, as assessed by the BDI/TDI from baseline to Week 24

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Frequency and severity of adverse events during the 24-week placebo-controlled period
- Incidence of ATAs against lebrikizumab throughout the study
- Frequency and severity of adverse events during the safety follow-up period

Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Predose trough (C_{min}) serum lebrikizumab concentrations at Weeks 4 and 12 ($C_{min,Wk4}$ and $C_{min,Wk12}$)
- Serum lebrikizumab concentration at Week 24 ($C_{min,Wk24}$)
- Elimination half-life ($t_{1/2}$)

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Change from baseline in blood eosinophils, serum periostin, IgE, CCL-13, CCL-17, and CCL-18
- Absolute change in pre-bronchodilator FEV_1 (liters) from baseline to Week 4
- Change in the 6MWT distance from baseline to Week 24
- Change in the body mass index, airflow obstruction, dyspnea and exercise capacity (BODE) index from baseline to Week 24
- Change in COPD rescue medication use from baseline to Week 24

Investigational Medicinal Products

Test Product (Investigational Drug)

Study drug (lebrikizumab or placebo) will be supplied by the Sponsor in a prefilled syringe. During the 24-week placebo-controlled period, all patients will receive a single SC injection at each dosing visit via prefilled syringe. The prefilled syringe of active drug product will be supplied as sterile liquid formulations at a concentration of 125 mg/mL lebrikizumab. The formulation of the active drug also contains histidine acetate (20 mM), sucrose (60 mg/mL), polysorbate 20 (approximately 0.03%), and Sterile Water for Injection, USP, pH 5.4–6.0. The placebo will be supplied by the Sponsor as a sterile liquid formulation. Each prefilled syringe of placebo will contain Sterile Water for Injection with histidine acetate (20 mM), sucrose (75 mg/mL), and polysorbate 20 (approximately 0.03%), pH 5.4–6.0. Prefilled syringes of study drug and placebo should be refrigerated at 2°C–8°C and protected from excessive light and heat. Prefilled syringes should not be frozen, shaken, or stored at room temperature.

Prefilled Syringe Configuration

Prefilled syringes of study drug will be provided assembled with needle safety devices. Prefilled syringes will be labeled "Lebrikizumab or placebo."

Each prefilled syringe of active study drug contains 1 mL of sterile liquid at a concentration of 125 mg/mL lebrikizumab. The 1-mL volume injection of active drug corresponds to 125 mg of lebrikizumab. Each prefilled syringe of placebo contains 1 mL of sterile placebo formulation.

Non-Investigational Medicinal Products

All patients will continue their COPD therapy as recommended in published COPD guidelines (GOLD 2015). Required COPD inhaler therapy for this study includes bronchodilator medication consisting of LABA or LAMA and ICS therapy.

Statistical Methods

Primary Analysis

The primary efficacy endpoint and each secondary efficacy endpoint will each be performed separately within an appropriate regression model (one per endpoint) as specified below in the protocol. All models (except for time to first severe or moderate COPD exacerbation) will include as covariates: treatment group, biomarker subgroup (as defined in Section 6), treatment group by biomarker subgroup interaction, baseline history of COPD exacerbations within the last 12 months (1, >1 event), baseline COPD medications (double vs triple therapy), smoking status (current, former), bronchodilator reversibility (present, absent), and geographical region (American Continent, ROW) as covariates. The study is sized to obtain point estimates and confidence intervals for treatment group differences *within* the biomarker-high subgroup, but not to detect treatment efficacy differences *between* biomarker-high and biomarker-low subgroups (test of biomarker subgroup by treatment group interaction effect).

All continuous endpoints measured at multiple visits will be analyzed using a mixed-effect model repeated measurement (MMRM) model. All such models will in addition to the above covariates include visit, visit by treatment group interaction, visit by biomarker subgroup interaction, biomarker subgroup by treatment group interaction, treatment group by visit interaction, and three-way visit by biomarker subgroup by treatment group interaction as covariates. Therefore, missing data will be handled by the model under the missing-at-random assumption without need for imputation for early discontinuation.

The primary and secondary objectives in this study will be assessed in the biomarker-high population. Models will include both biomarker-high and biomarker-low groups. Treatment effect estimates in both biomarker groups will be provided.

Testing of the effect of lebrikizumab compared with placebo on a given endpoint within both biomarker-high and biomarker-low subgroups will be performed via a Wald at the two-sided $\alpha = 0.20$ level of the between-group least squares mean (LSM) differences with the LSMESTIMATE statement in SAS. Two tests for each endpoint (one treatment comparison per biomarker subgroup) will be performed and p-values reported with no adjustment for multiplicity. Point and interval estimates of LSMs within each treatment/biomarker subgroup combination will be presented.

The primary efficacy endpoint for this study is the absolute change in pre-bronchodilator FEV_1 (volume) from baseline to Week *12*. The baseline pre-bronchodilator FEV_1 measurement is defined as the last spirometry measurement prior to or on the day of randomization. The primary endpoint will be analyzed using a MMRM model as specified in protocol *and assessments after Week 12 will be excluded from the MMRM model.* Baseline pre-bronchodilator FEV_1 will be included as an additional covariate. *Missing data will be handled by the model under the missing-at-random assumption without need for imputation for early discontinuation.* The treatment effect will be tested within each biomarker subgroup according to the procedure specified in protocol. *Point and interval estimates of the change from baseline of pre-bronchodilator FEV1 within each treatment group/biomarker group combination as well as of the difference in change from baseline of pre-bronchodilator FEV1 between treatment groups within each biomarker subgroup will be presented. A sensitivity analysis with respect to protocol adherence will be performed by excluding data collected more than 6 weeks after last study drug administration.*

The assessment optimal cutoff for the biomarker-high group will be explored.

Determination of Sample Size

The study will enroll approximately 300 patients. Patients will be randomized in a 1:1 ratio to receive treatment with either lebrikizumab 125 mg or placebo every 4 weeks, in addition to standard-of-care COPD medications. The sample size of 150 patients per arm provides at least 80% power to detect a 77 mL (approximately 5.7 percent change from baseline) difference in pre-bronchodilator FEV_1 change from baseline at Week*s 12 and* 24 between treatment groups among patients within the biomarker-high subgroup (75 biomarker-high patients in the lebrikizumab arm compared with 75 biomarker-high patients in the placebo arm) under the following assumptions:

- The absolute change from baseline at Week *12* in pre-bronchodilator FEV_1 is normally distributed with a standard deviation of 210 mL
- Two-sided alpha is 0.20
- Prevalence of the biomarker-high subgroup is at least 50% of the sample
- Drop-out rate at Week *12* is 10%, leading to a 10% loss of information

The assumed standard deviation of 210 mL was obtained by taking the square root of the sample-size weighted average of pooled population variance estimates as reported on clinicaltrials.gov. These COPD trials were selected because of the similarity of inclusion/exclusion criteria to the current trial.

Interim Analyses

The interim safety analyses will be performed periodically and reviewed by the IMC.

*T*he Sponsor may choose to conduct up to two interim efficacy analyses. The decision to conduct an optional interim efficacy analysis and the timing of the interim efficacy analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim efficacy analysis. The interim efficacy analysis will be performed and interpreted by members of the Sponsor study team and appropriate senior management personnel who will be unblinded at the treatment group level. Access to treatment assignment information will follow the Sponsor's standard procedures.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
6MWT	six-minute walk test
AESI	adverse event of special interest
ATA	anti-therapeutic antibody
ATS	American Thoracic Society
BODE	the body mass index, airflow obstruction, dyspnea and exercise capacity
Borg CR10 Scale®	Borg Category Ratio 10 Scale®
BDI	Baseline Dyspnea Index
C_{min}	minimum concentration
COPD	chronic obstructive pulmonary disease
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DT	dosing termination
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ePRO	electronic patient-reported outcome
ERS	European Respiratory Society
ET	early termination
EtM	events to be monitored
EXACT	EXAcerbations of Chronic Pulmonary Disease Tool
FDA	U.S. Food and Drug Administration
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroids
IM	intramuscular
IMC	Internal monitoring committee
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IV	intravenous

Abbreviation	Definition
IRB	Institutional Review Board
IxRS	interactive voice/Web–based response system
LABA	long-acting β-agonist
LAMA	long-acting muscarinic antagonist
LPLV	last patient, last visit
LSM	least squares mean
LTRA	leukotriene receptor antagonist
mITT	modified intent-to-treat
mMRC	modified Medical Research Council
MMRM	mixed-effect model repeated measurement
NCI	National Cancer Institute
PD	pharmacodynamics
PK	pharmacokinetics
PRO	patient-reported outcome
RCR	Roche Clinical Repository
ROW	rest of world
SC	subcutaneous
SGRQ-C	Saint George's Respiratory Questionnaire–COPD
SNP	single nucleotide polymorphism
SPA	Statistical Programming and Analysis
TDI	Transition Dyspnea Index
Th1	Type 1 helper T cell
Th2	Type 2 helper T cell
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ON COPD

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is usually progressive and associated with chronic airway inflammation (GOLD 2015). The airflow limitation is caused by a mixture of small airways disease and parenchymal destruction (emphysema) and may be associated with gas exchange abnormalities and hyperinflation (GOLD 2015). Clinically, the characteristic symptoms of COPD are dyspnea, cough, and sputum production.

COPD is the fourth leading cause of death in the world and projected to become the third leading cause of death by 2030 (WHO 2013). Worldwide estimation of the overall prevalence of ≥ Stage 2 (moderate) COPD is 10.1% (Buist et al. 2007). COPD is caused by long-term exposure to inhaled noxious gases and particles. Cigarette smoke accounts for more than 90% of cases in developed countries. COPD usually occurs in patients over the age of 40 years and is more common in men.

COPD exacerbations are associated with increased airway and systemic inflammation leading to a worsening of respiratory symptoms. COPD exacerbations account for the greatest proportion of the total COPD burden on the healthcare system, are a major cause of morbidity and mortality, and contribute to reduced quality of life (Seemungal et al. 1998; Garcia-Aymerich et al. 2003; Soler-Cataluña et al. 2005). Exacerbations may be associated with an increased rate of disease progression as measured by forced expiratory volume in 1 second (FEV_1) decline over time (Siva et al. 2007; Donaldson et al. 2002). Frequent acute exacerbations are an independent risk factor for all-cause mortality in COPD and patients with a history of exacerbations are at increased risk for future exacerbations (Soler-Cataluña et al. 2005; Halpin et al. 2012; Lange et al. 2012; Maleki-Yazdi et al. 2012). Therefore, interventions that reduce the frequency of exacerbations would be expected to have beneficial impact on morbidity, healthcare costs, and possibly on mortality (Anzueto et al. 2009).

COPD has been recognized as a progressive disease characterized by an accelerated rate of decline in FEV1 over time (GOLD 2015). COPD is a heterogeneous disorder comprising a number of different phenotypes, including airflow limitation and exacerbations. The extent of inflammation, fibrosis, and luminal exudates in small airways is correlated with the reduction in FEV_1 and FEV_1/forced vital capacity (FVC) ratio, and likely with the accelerated decline in FEV_1 (Celli et al. 2008). This peripheral airway obstruction progressively traps air during expiration resulting in hyperinflation. Gas exchange abnormalities result in hypoxemia and hypercapnia and have several mechanisms in COPD. In general, gas transfer for oxygen and carbon dioxide worsens as the disease progresses (GOLD 2015).

Current treatment options for COPD include non-pharmacologic and pharmacologic measures. Smoking cessation is a key intervention for patients who continue to smoke

and has the greatest potential to impact the natural course of COPD. Pharmacologic treatment options include inhaled bronchodilators (beta-agonists and anticholinergics), inhaled and systemic corticosteroids, methylxanthines, and phosphodiesterase inhibitors. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline (GOLD 2015) describes 4 patient groups based on history of exacerbations, FEV_1, and symptoms. Patients with a history of exacerbations and/or reduced FEV_1 are considered at higher risk for future adverse outcomes and require more intensive therapy. First-line recommendations include inhaled corticosteroids (ICS) plus long-acting β-agonists (LABA) or long-acting muscarinic antagonists (LAMA) (Group C) and ICS plus LABA and/or LAMA (Group D). ICS/LABA is more effective than the individual components in reducing exacerbations and improving lung function and health status in moderate to very severe COPD (Mahler et al 2002; Szafranski et al. 2003; Calverly et al. 2003; Drummond et al. 2008; Doherty et al. 2012). ICS tested in completed clinical trials were medium to high doses and were associated with a risk of pneumonia (Crim et al. 2015; Kew and Seniukovich 2014; Calverly et al. 2011; Singh et al. 2009).

COPD has typically been considered to have a pattern of airway inflammation that is distinct from asthma, with infiltration of T cells that are predominantly Type 1 helper (Th1), neutrophils, and macrophages. More recent studies suggest that approximately 20%–30% of patients with COPD have measurable sputum eosinophilia and 30%–40% of patients have blood eosinophil levels comparable to patients with eosinophilic asthma (Bafadhel et al. 2011; Siva et al. 2007; Singh et al. 2014). Analysis of sputum inflammatory mediators also suggests that a proportion of patients have overlapping features of asthma and COPD (Ghebre et al. 2015).

1.2 BACKGROUND ON LEBRIKIZUMAB

Lebrikizumab is a humanized monoclonal antibody (huIgG4) with an Fc region modification in the hinge region for increased stability that binds specifically to soluble interleukin 13 (IL-13). It has high affinity and neutralizes the functional activities of IL-13 with high potency.

Current data support an important role for IL-13 in Type 2 helper T cell (Th2)-driven inflammation, including airway mucus hypersecretion and small airway obstruction. Transgenic mouse models suggest a central role for IL-13 in mucus hypersecretion and emphysema-like peripheral alveolar destruction phenotypes which mimic aspects of COPD (Zhu et al. 1999; Zheng et al. 2000). IL-13 promotes differentiation of ciliated epithelial cells into goblet cells, which produce mucins that are complexed with water and released into the airway lumen. In models of non-Th2 driven airway inflammation, mucus production also appears to be IL-13 dependent (Kim et al. 2008). Lymphocytes from bronchoalveolar lavage and sputum from patients with COPD have shown increased intracellular IL-13 expression (Barcelo et al. 2006; Eickmeier et al. 2010) and elevated plasma IL-13 levels have been associated with lower lung function and worsening small airways disease (Lee et al. 2007; Curran and Cohn 2010). IL-13

stimulates eosinophilic inflammation, and recent studies suggest that a subgroup of COPD patients have airway eosinophilia (Bafadhel et al. 2011; Siva et al. 2007; Singh et al. 2014). In addition to the established role for IL-13 in recruiting eosinophils to the airways, IL-13 can also exert direct effects on airway structural cells leading to fibrosis and airway remodeling. While the underlying disease mechanisms of COPD are heterogenous, because IL-13 has pleiotropic effects, treatment with lebrikizumab may attenuate the symptoms and progression of COPD.

See the Lebrikizumab Investigator's Brochure for details about nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

A total of 773 individual subjects, including 661 patients with asthma, have received at least one dose of lebrikizumab as part of ten completed clinical studies. Treatment with lebrikizumab appeared to be well tolerated during these studies.

Efficacy data were obtained in five completed Phase II studies in patients with asthma (Studies ILR4544g, ILR4646g, ILR4660g, GB28762, and GB28764):

- Study ILR4544g: a small Phase II study that demonstrated benefit in reducing the response to inhaled aeroallergen in patients with mild asthma (not taking ICS therapy)
- Study ILR4646g: a Phase IIa study that demonstrated the benefit of IL-13 inhibition with lebrikizumab as measured by change in FEV_1 in patients with uncontrolled asthma despite treatment with ICS therapy. There was a trend for a reduced rate of severe asthma exacerbations, although the 95% confidence intervals did not exclude zero.
- Study ILR4660g: a Phase II study in patients with asthma who were not being treated with ICS therapy demonstrated that lebrikizumab treatment was associated with a small relative increase in FEV_1 as well as a reduction in the rate of treatment failures (i.e., events requiring treatment with corticosteroids) compared with placebo
- Studies GB27862 and GB27864: lebrikizumab was assessed in two replicate Phase IIb studies in patients with uncontrolled asthma who were on ICS and a second controller medication. Treatment with lebrikizumab was associated with a reduction in the rate of exacerbations compared with placebo. The effect of lebrikizumab on exacerbation rate was greater in periostin-high patients compared with periostin-low patients. The effect of lebrikizumab on FEV_1 was also greater in periostin-high patients compared with periostin-low patients.

Pharmacodynamic (PD) evaluation from these studies also provided evidence that lebrikizumab inhibits the activity of IL-13, as reflected by fractional exhaled nitric oxide, chemokine ligand (CCL)-13, CCL-17, and IgE changes. The biomarker serum periostin was evaluated in Studies ILR4646g, GB27862, and GB27864, and baseline levels of $\geq$50 ng/mL were shown to be predictive of the patients who have a clinically meaningful benefit from lebrikizumab therapy (Corren et al. 2011).

In addition to the efficacy of lebrikizumab, the reported safety data from the completed studies revealed no clinically important safety risks. In this population of patients with asthma, lebrikizumab appeared to have a favorable benefit-risk profile.

In patients with COPD and high blood eosinophil counts and/or periostin levels at baseline, the underlying disease biology may share similarities to Th2-driven asthma. A recent Phase IIa study with benralizumab, an anti-IL-5R monoclonal antibody, suggested *a beneficial effect* on FEV_1 and a trend towards a reduction in the rate of acute COPD exacerbations in patients with blood eosinophils $\geq$300 cells/μL (Brightling et al. 2014). Given the potential similarity in disease biology, lebrikizumab may also provide benefit in a COPD population. Therefore, this Phase II study aims to evaluate the safety, efficacy, and pharmacokinetics of lebrikizumab in patients with COPD, as well as the utility of baseline serum periostin and blood eosinophil levels in identifying patients who are most likely to receive clinical benefit.

For additional information, refer to the Lebrikizumab Investigator's Brochure.

2. OBJECTIVES

2.1 EFFICACY OBJECTIVES

The primary efficacy objective for this study is:

- To evaluate the efficacy of lebrikizumab compared with placebo in improving lung function, as measured by the absolute change in pre-bronchodilator FEV_1 in patients with COPD and a history of exacerbations *in the biomarker-high group (elevated* serum periostin and blood eosinophils*) and biomarker-low group.*

The secondary efficacy objective for this study is as follows:

- To evaluate *in the biomarker high and biomarker-low groups* the rate of moderate and severe COPD exacerbations, change in post-bronchodilator FEV_1, time to first exacerbation, and change in health-related quality of life and change in symptoms as measured by the Saint George's Respiratory Questionnaire for COPD patients (SGRQ-C), EXAcerbations of Chronic Pulmonary Disease Tool (EXACT), and Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI)

2.2 SAFETY OBJECTIVES

The safety objective for this study is as follows:

- To evaluate the safety of lebrikizumab compared with placebo in patients with COPD and a history of exacerbations, focusing on the nature, frequency, and severity of serious and non-serious adverse events

2.3 PHARMACOKINETIC OBJECTIVES

The pharmacokinetic (PK) objective for this study is as follows:

- To evaluate serum lebrikizumab concentrations *and PK parameters* in patients with COPD and a history of exacerbations

2.4 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- *To evaluate the change in the six-minute walk test (6MWT) from baseline to Week 24*
- To evaluate IL-13–related and COPD–related PD biomarkers, changes in measures of lung function, and rescue medication use

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This is a Phase II, randomized, multicenter, double-blind, placebo-controlled, parallel-group clinical trial of lebrikizumab in patients with COPD and a history of exacerbations who are treated with ICS and at least one long-acting bronchodilator inhaler medication (LABA or LAMA). Patients receiving additional background COPD medications are permitted to enter the study. This study will also assess baseline levels of serum periostin and baseline blood eosinophil counts as predictive biomarkers for identifying patients who may achieve clinically meaningful efficacy. Patients will be considered biomarker-high if the baseline serum periostin is $\geq$50 ng/mL or baseline blood eosinophil count is $\geq$300 cells/μL. The study consists of a screening period, a placebo-controlled period, and a safety follow-up period.

Written informed consent for participation in the study must be obtained before performing any study-specific tests or evaluations. Patients then commence a screening period of approximately 14 days that includes a screening visit (Visit 1) as well as a final assessment of eligibility prior to randomization at Visit 2. During the screening period, patients will be assessed for adherence with their current COPD background therapy, their ability to use the equipment necessary for monthly clinic visits throughout the study, and the degree of dyspnea, and will be evaluated to determine if they meet all other eligibility criteria.

Patients may be eligible for rescreening up to two additional times*, with all inclusion and exclusion criteria being re-assessed*.

After screening has been completed, eligible patients will be randomized in a 1:1 ratio to receive double-blind treatment with subcutaneous (SC) lebrikizumab 125 mg or placebo, administered every 4 weeks. Randomization will be stratified by biomarker status (biomarker high [baseline blood eosinophil counts $\geq$300 cells/μL or periostin $\geq$50 ng/mL] or biomarker low [baseline blood eosinophil counts $<$300 cells/μL and periostin $<$50 ng/mL]), history of moderate/severe COPD exacerbations within the last 12 months (1, $>$1 event), smoking status (current, former), geographical region*(American Continent, rest of world [ROW]),* and participation in the computed tomography (CT) scan substudy (yes, no).

The first dose of study drug *should* be administered as *close to* randomization *as possible* (Visit 2 [Day 1]), and dosing will be repeated once every 4 weeks during a 24-week placebo-controlled period (for a total of 6 doses). Patients will continue on stable doses of their standard-of-care therapy that must include ICS therapy and a long-acting bronchodilator inhaler medication, in addition to receiving double-blind study drug, for *the duration of the study*.

Safety, efficacy, and patient-reported outcome (PRO) measures will be assessed throughout the placebo-controlled period as detailed in the schedule of assessments (see Appendix 1). The primary efficacy endpoint is the absolute change in pre-bronchodilator FEV_1 (liters) from baseline to Week *12*.

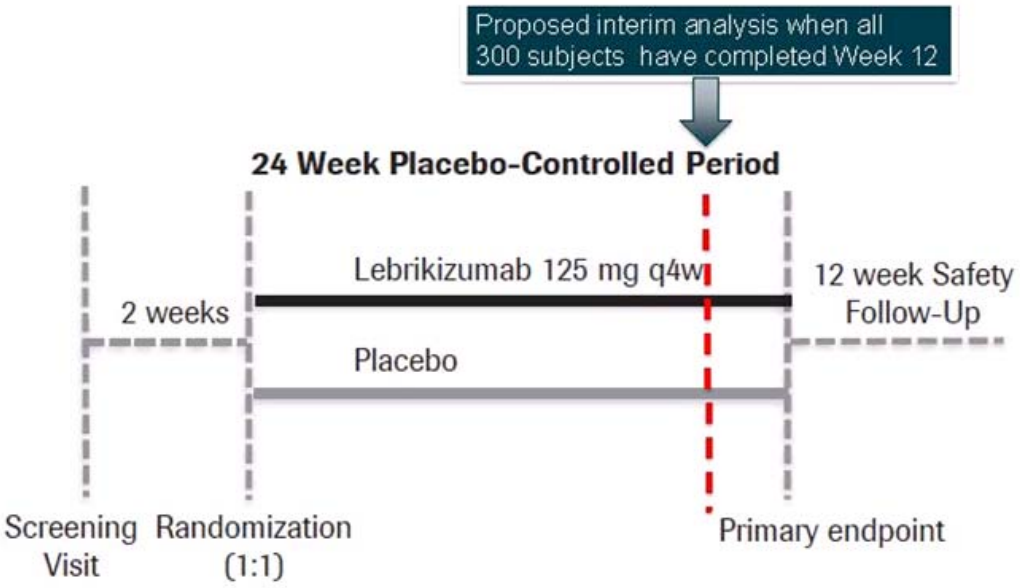
After the last dose of study drug in the placebo-controlled period, all patients will be followed for safety for 16 weeks (approximately 4 half-lives of lebrikizumab). This includes the 4 weeks after the final dose during the placebo-controlled period and a 12-week safety follow-up period. The safety follow-up period is detailed in the schedule of assessments.

All patients who discontinue study drug early in the placebo-controlled period will be asked to continue study assessments in the placebo-controlled period and then complete the safety follow-up period. Patients who are unwilling or unable to continue with assessments in the placebo-controlled period will complete a dosing termination (DT) visit and then enter safety follow-up.

Total participation in the study starting from randomization at Visit 2 (Day 1), including the 24-week placebo-controlled period and 12-week safety follow-up period, may be as long as 36 weeks (see Appendix 1).

The study design is depicted in Figure 1.

Figure 1 Study Schema



q4w = every 4 weeks

3.2 END OF STUDY

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs. The LPLV is expected to occur *approximately* 36 weeks after the last patient is randomized into the study. This timeframe includes a 24-week placebo-controlled period and a 12-week safety follow-up period.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Lebrikizumab Dose and Schedule

The selected Phase II dose *for COPD* is 125 mg given by SC injection every 4 weeks. The dosing frequency is supported by the half-life of lebrikizumab of approximately 25 days as well as the safety and efficacy data from Phase II asthma studies with the same dosing frequency.

In the Phase II asthma studies, lebrikizumab 250 mg, 125 mg, and 37.5 mg have demonstrated *effects* in reducing the rate of asthma exacerbations and improving FEV_1 in moderate-severe asthma patients. In the Phase II study ILR4646g, there was a trend for the 250-mg dose of lebrikizumab (the only dose evaluated) to reduce the rate of severe asthma exacerbations in periostin-high patients whose asthma was uncontrolled despite treatment with ICS therapy. In a Phase II dose-ranging study, Study ILR4660g, of lebrikizumab in patients not treated with ICS therapy, a similar magnitude of FEV_1 improvement and similar reduced risk for treatment failure was observed at the 125- and 250-mg dose levels. In the Phase IIb studies GB27862 and GB27864, the 250-mg dose

did not provide incremental benefit above the treatment benefit seen with 125-mg on rate of asthma exacerbations or FEV_1 in periostin-high patients. While the 37.5 mg dose demonstrated *an effect* on rate of exacerbations, the confidence intervals were wide, and the 37.5-mg dose demonstrated lower benefit on mean placebo-corrected FEV_1 improvement. Based on these data, a dose of 125 mg is expected to demonstrate clinical efficacy in the ongoing Phase III asthma trials.

There are reports of raised IL-13 (Lee et al. 2007) and periostin (Fingleton et al. 2014) in COPD. As with asthma, the findings are variable, although there is consensus that a subpopulation of patients with COPD appears to exhibit elevations of these and other markers of Th2 disease and to respond to ICS. The therapeutic response to ICS in these patients appears to be associated with reduction in periostin (Fingleton et al. 2014).

The 125-mg dose, which *has been shown* to be effective in patients with asthma, is expected to maintain sufficiently high drug levels to neutralize IL-13 in the lung of COPD patients, and has, therefore, been selected for this study.

3.3.2 Rationale for Patient Population

There is a high unmet need and limited therapeutic options for patients with intermittent acute COPD exacerbations and persistent dyspnea, despite adherence with guidelines-based standard-of-care therapy. In this study, the target population is patients with COPD and a history of exacerbations who continue to experience dyspnea despite treatment with ICS and a long-acting bronchodilator (LABA or LAMA). This clinical trial is designed to test the efficacy and safety of lebrikizumab in this patient population.

ICS and inhaled bronchodilators (LABAs and LAMAs) are currently the most effective available therapies to improve dyspnea and prevent future exacerbations in patients with a history of exacerbations. Increasing ICS doses beyond approved doses for COPD has not been evaluated in large clinical trials and oral corticosteroid therapy is associated with substantial side effects. The GOLD guideline (GOLD 2015) includes several options for additional controller medications, which reflect the heterogeneity of clinical response to each medication class. Additional therapy with phosphodiesterase-4 inhibitors and theophylline may be considered as treatment in patients who meet the approved indication and will be permitted during this study.

The definition of COPD exacerbation used in this study is consistent with published guidelines that define a patient population with unmet medical need. Patients with exacerbations despite treatment with ICS and bronchodilator therapy are at risk for future exacerbations and adverse health outcomes. Persistent dyspnea as defined by the modified Medical Research Council (mMRC) dyspnea score during screening identifies a patient population with incomplete control of symptoms.

All patients who will be considered for participation will have a physician diagnosis of COPD for at least 12 months prior to screening. This diagnosis will be supported by demonstration of post-bronchodilator airways obstruction as defined by the FEV_1/FVC ratio at screening. Patients will be assessed for adherence to their chronic controller therapy via response to daily questions and must demonstrate a specific level of adherence to be eligible for study participation. Patients will also be instructed on proper inhaler technique and the importance of adherence to standard-of-care therapy. Patients will be assessed for comorbidities that may contribute to the clinical presentation of COPD and specific comorbidities will be captured via targeted medical history at baseline. All eligible patients will have a history of at least one moderate/severe COPD exacerbation in the 12 months prior to screening.

3.3.3 Rationale for Control Group

A placebo-treated control group will be used in this study to assess the differences in exacerbations, pulmonary function, symptoms, and safety compared with patients who receive lebrikizumab. The use of a control group is necessary given the inherent variability in COPD exacerbations, patients' lung function, the recognized placebo response in COPD trials, and the use of subjective assessments such as the PRO instruments. Patients in the control group will undergo the same study assessments as the lebrikizumab-treated patients. All patients will continue to receive standard-of-care inhaled therapy in addition to study drug throughout the study.

3.3.4 Rationale for Biomarker Assessments

Periostin is induced by IL-13 in lung fibroblasts and bronchial epithelial cells. The expression of periostin in the airway of patients with asthma is correlated with bronchial mucosal IL-13 expression and with the presence of eosinophils in the airways. Periostin can be detected in peripheral blood and has been identified as a candidate biomarker useful for identifying asthma patients most likely to receive benefit from lebrikizumab (Corren et al. 2011). A periostin assay is being developed as a companion diagnostic assay under the established design and manufacturing controls at Roche Professional Diagnostics. The assay, Elecsys® periostin, is an automated electrochemiluminescence immunoassay based on the sandwich principle and intended for use on the Cobas e601. A baseline level of serum periostin $\geq$50 ng/mL may be predictive of clinically meaningful efficacy with lebrikizumab treatment in asthma (Study ILR4646g; Corren et al. 2011).

Recently published literature in COPD indicates that airway expression of a Th2 gene signature that includes periostin (POSTN) and is well correlated with Th2-associated clinical characteristics in an asthma dataset can be used to identify a COPD subgroup with Th2 inflammation (Christenson et al. 2015). This supports the growing evidence that similar processes leading to airflow obstruction in asthma may occur in at least a COPD subgroup and that periostin may be a useful biomarker to identify this subgroup.

Published literature in asthma indicates that eosinophils in the lung are also linked to Th2 and IL-13 activity suggesting that blood eosinophil counts might be another biomarker that can predict response to anti-IL-13 therapies (Walford and Doherty 2014; Horie et al. 1997; Luttmann et al. 1996; Bochner et al. 1995; Pope et al. 2001; Truyen et al. 2006; Woodruff et al. 2009). In COPD, there are multiple reports that support the diagnostic value of eosinophil counts. Blood eosinophil counts can identify patients most likely to benefit from corticosteroid treatment (Bafadhel et al. 2012). A targeted strategy to normalize sputum eosinophilia >3% in COPD with use of inhaled corticosteroids reduced the frequency of severe COPD exacerbation-related hospital admissions (Siva et al. 2007). In addition, benralizumab treatment resulted in greater FEV_1 improvement and exacerbation rate reduction in patients with COPD with baseline blood eosinophil levels of ≥ 300 cells/μL as compared with patients with < 300 cells/μL (Brightling et al. 2014). The distribution of blood eosinophil levels in COPD was recently evaluated by Tran et al. (2014) using data from the National Health and Nutrition Examination Surveys (2007–2010). This analysis found that approximately 71% and 40% of patients with COPD had blood eosinophil levels of ≥200 cells/μL and ≥300 cells/μL, respectively, suggesting that 300 cells/μL is close to the median of the blood eosinophil distribution in patients with COPD.

Taken together, higher levels of periostin or eosinophil counts may be reflective of underlying IL-13 driven airway inflammation and, therefore, these biomarkers may be useful in identifying patients most likely to respond to lebrikizumab. These two biomarkers may identify populations that are not completely overlapping and each biomarker may provide independent information. Therefore, this study will assess the diagnostic value of baseline levels of either or both serum periostin and blood eosinophil counts as predictive biomarkers for clinically meaningful efficacy of lebrikizumab.

Biomarker-high patients will be defined as patients with baseline periostin ≥50 ng/mL or blood eosinophils ≥300 cells/μL, and patients with baseline periostin <50 ng/mL and blood eosinophils <300 cells/μL will be considered biomarker-low. *Other ranges might be explored at the end of the study.*

Blood samples will be collected at baseline and throughout the study to assess the relationship between periostin, blood eosinophils, and other IL-13/COPD–related biomarkers, including but not limited to *total* IgE, CCL-13, CCL-17, CCL-18*, and fibrinogen* and changes in clinical status. If novel IL-13 or COPD-related biomarkers are identified, they may be measured from stored serum.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

Each efficacy endpoint will be analyzed separately in biomarker-high and biomarker-low patients (see Section 6).

The primary efficacy endpoint for this study is as follows:

- Absolute change in pre-bronchodilator FEV_1 (liters) from baseline to Week *12*

The secondary efficacy endpoints are as follows:

- Rate of moderate/severe COPD exacerbations during the 24-week placebo-controlled period

  A moderate COPD exacerbation is defined as new or increased COPD symptoms (e.g., dyspnea, sputum volume, and sputum purulence) for at least 2 consecutive days that lead to treatment with systemic corticosteroids and/or antibiotics

  A severe COPD exacerbation is defined as new or increased COPD symptoms (e.g., dyspnea, sputum volume, and sputum purulence) for at least 2 consecutive days that lead to hospitalization

- Absolute change in post-bronchodilator FEV_1 (liters) from baseline to Week 24
- *Absolute change in pre-bronchodilator FEV_1 (liters) from baseline to Week 24*
- Time to first COPD exacerbation during the 24-week placebo-controlled period
- Change in health-related quality of life, as assessed by the overall score of the SGRQ-C, from baseline to Week 24
- Change in COPD symptoms as measured by the overall score on the EXACT from baseline to Week 24
- Change in cough and sputum as measured by the cough and sputum domain of the EXACT from baseline to Week 24
- Change in dyspnea, as assessed by the BDI/TDI from baseline to Week 24

3.4.2 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Frequency and severity of adverse events during the 24-week placebo-controlled period
- Incidence of ATAs against lebrikizumab throughout the study
- Frequency and severity of adverse events during the safety follow-up period

3.4.3 Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Predose trough (C_{min}) serum lebrikizumab concentrations at Weeks 4 and 12 ($C_{min,Wk4}$ and $C_{min,Wk12}$)
- Serum lebrikizumab concentration at Week 24 ($C_{min,Wk24}$)
- Elimination half-life ($t_{1/2}$)

3.4.4 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Change from baseline in blood eosinophils, serum periostin, IgE, CCL-13, CCL-17, and CCL-18
- Absolute change in pre-bronchodilator FEV_1 (liters) from baseline to Week 4
- Change in the 6MWT distance from baseline to Week 24
- Change in the body mass index, airflow obstruction, dyspnea and exercise capacity (BODE) index from baseline to Week 24
- Change in COPD rescue medication use from baseline to Week 24

4. MATERIALS AND METHODS

4.1 PATIENTS

The study will enroll patients with COPD and a history of at least 1 moderate/severe exacerbation requiring treatment with corticosteroids in the 12 months prior to screening and persistent dyspnea despite treatment with ICS and a long-acting bronchodilator medication (LABA or LAMA). Patients receiving additional COPD medications are permitted to enter the study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Able and willing to provide written informed consent and to comply with the study protocol
- Age 40–*80* years old at Visit 1
- Able and willing to use the electronic device for patient-reported data collection
- Documented history of COPD diagnosis for ≥12 months prior to Visit 1
- Post-bronchodilator $FEV_1/FVC < 0.70$ at Visit 1 or Visit 2
- Post-bronchodilator $FEV_1 < 80\%$ predicted at Visit 1 or Visit 2
- Documented history of one or more acute COPD exacerbations that required treatment with systemic corticosteroids and/or *antibiotics or* hospitalization within 12 months prior to Visit 1
- Current *tobacco* smoker or former smoker *(having stopped smoking for at least 6 months prior to Visit 1)* with a history of *smoking* ≥10 pack-years *(20 cigarettes/day for 10 years). A former smoker may not have used inhaled tobacco products or inhaled marijuana within the past 3 months (e.g., cigarettes, cigars, electronic cigarettes, or pipe tobacco).*
- On ICS therapy for ≥6 months prior to Visit 1
- On an eligible bronchodilator medication (LABA, LAMA, or both) for ≥6 months prior to Visit 1

- Chest X-ray or CT scan within 6 months prior to Visit 1 or chest X-ray during the screening period (prior to Visit 2) that confirms the absence of clinically significant lung disease besides COPD
- Demonstrated adherence with background COPD inhaler medication during the screening period. Adherence is defined as patients responding affirmatively that they have taken their inhaler therapy ≥70% of days during the screening period (Visits 1–2), as recorded in their eDiary
- For women who are not postmenopausal (≥12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined contraceptive methods that result in a failure rate of <1% per year for the duration of the study (during the placebo-controlled period and the safety follow-up period) *(see Appendix 8)*

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the lebrikizumab injection
- History of clinically significant pulmonary disease other than COPD
- Diagnosis of alpha-1-antitrypsin deficiency
- Lung volume reduction surgery or procedure within 12 months prior to Visit 1
- Supplemental oxygen requirement >2 L/min at rest or with exertion
- Current diagnosis of asthma
- Patients participating in, or scheduled for, an intensive COPD rehabilitation program (patients who are in the maintenance phase of a rehabilitation program are eligible)
- Maintenance oral corticosteroid therapy, defined as daily or alternate-day oral corticosteroid maintenance therapy, within 3 months prior to Visit 1
- Treatment with systemic (oral, intravenous [IV], or intramuscular [IM]) corticosteroids within 4 weeks prior to Visit 1 or during the screening period for any reason, including an acute exacerbation event
- Unstable ischemic heart disease, arrhythmia, cardiomyopathy, or other relevant cardiovascular disorder that, in the opinion of the investigator, may put the patient at risk or negatively affect the study outcome
- Any infection that resulted in hospital admission for ≥24 hours *and/*or treatment with *oral,* IV*,* or IM antibiotics within 4 weeks prior to Visit 1 or during screening
- Upper or lower respiratory tract infection within 4 weeks prior to Visit 1 or during screening
- Active parasitic infection or *Listeria monocytogenes* infection within 6 months prior to Visit 1 or during screening

- Active tuberculosis requiring treatment within 12 months prior to Visit 1. Patients who have completed treatment for tuberculosis at least 12 months prior to Visit 1 and have no evidence of recurrent disease are permitted.
- Known immunodeficiency, including but not limited to HIV infection
- Evidence of acute or chronic hepatitis or known liver cirrhosis
- AST, ALT, or total bilirubin elevation $\geq 2.0 \times$ the upper limit of normal (ULN) during screening
- Clinically significant abnormality on screening ECG or laboratory tests (hematology, serum chemistry, and urinalysis) that, in the opinion of the investigator, may pose an additional risk in administering study drug to the patient
- Known current malignancy or current evaluation for a potential malignancy
- Other clinically significant medical disease that is uncontrolled despite treatment, that is likely, in the opinion of the investigator, to impact the patient's ability to participate in the study or impact the study efficacy or safety assessments
- History of alcohol or drug abuse that would impair or risk the patient's full participation in the study, in the opinion of the investigator
- Past and/or current use of any anti–IL-13 or anti–IL-4/IL-13 therapy, including lebrikizumab. Patients participating in a clinical trial that has not been unblinded should be assumed to have received the active drug.
- Treatment with an immunomodulatory or immunosuppressive monoclonal antibody (other than an anti–IL-13 or anti–IL-4/IL-13 therapy) within 6 months or 5 drug half-lives prior to Visit 1 (whichever is longer) or during screening. Patients participating in a clinical trial that has not been unblinded should be assumed to have received the active drug.
- Use of an immunomodulatory or immunosuppressive therapy (other than a monoclonal antibody or corticosteroids [see separate exclusion]) within 3 months or 5 drug half-lives prior to Visit 1 (whichever is longer) or during screening
- Use of other investigational therapy not described above within 4 weeks or 5 drug half-lives prior to Visit 1 (whichever is longer) or during screening. Patients participating in a clinical trial that has not been unblinded should be assumed to have received the active drug.
- Receipt of a live attenuated vaccine within 4 weeks prior to Visit 1 or during screening
- Pregnant or lactating
- Body weight < 40 kg

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Patients will be randomized to the treatment arms through the interactive voice/Web–based response system (IxRS). After written informed consent has been obtained, all patients will receive a screening number, which will be assigned by the IxRS. Following completion of the screening period and after all patient eligibility

requirements are confirmed at Visit 2 (Day 1), patients will be assigned a subject number (a different number from the screening number) and will be randomized in a 1:1 ratio to one of two treatment arms (lebrikizumab 125 mg or placebo every 4 weeks) for the placebo-controlled period. Patients *should* be randomized *as close as possible to* the day that treatment is to be initiated (Visit 2 [Day 1]).

Randomization will be stratified by biomarker status (biomarker high [baseline blood eosinophil levels $\geq$300 cells/μL or periostin $\geq$50 ng/mL], biomarker low [baseline blood eosinophil levels $<$300 cells/μL and periostin $<$50 ng/mL)], history of moderate/severe COPD exacerbations within the last 12 months (1, $>$1 event), smoking status (current, former), geographical region *(American Continent, ROW),* and participation in the CT substudy (yes, no). A permuted block randomization will be used to obtain an approximately 1:1 ratio between the two treatment arms within each stratum. At each dosing visit during the placebo-controlled treatment period, study treatment kits will be assigned via the IxRS. The placebo and active kits are filled and packaged to look identical. Patients and all study site personnel will be blinded to treatment assignment until all patients have either completed the study through the safety follow-up period or discontinued early from the study, the database is locked, and the study analyses are final. The Sponsor and its agents will be blinded to treatment assignment *until all subjects have either completed their Week 12 visit or discontinued from the placebo-controlled period early*, with the exception of the following agents who will not be blinded to treatment assignment during the study: IxRS service provider, bioanalytical laboratory personnel, and Internal Monitoring Committee (IMC) members. Treatment assignment will be unblinded *the Sponsor for the primary* analysis.

The primary analysis will be performed when all subjects have completed their Week 12 visit or discontinued from the placebo-controlled period early and after all data are in the database and the data have been cleaned and verified. To minimize biases, investigators, patients as well as the study team members other than those mentioned above will remain blinded at the patient level until the final database lock.

Study completion is defined as all subjects having completed safety follow-up through Week 36 or discontinued from the study early. Patients and all study site personnel will be blinded to periostin and other PD biomarker levels until study completion, except as described below. Sponsor study team members who have direct contact with study sites will remain blinded to individual periostin and blood eosinophil levels, but team members who do not interact with study sites may review individual pretreatment periostin and blood eosinophil levels for assessment of baseline study information and ongoing review of data quality. The Sponsor will remain blinded to individual post-treatment periostin and other post-treatment PD biomarker levels until *the primary analysis*. Eosinophil counts during screening will be reviewed by the sites as part of routine laboratory data review. Patients, all study site personnel, and the Sponsor will be blinded to eosinophil counts post-randomization except for clinically significant elevations in eosinophil counts which will be reported to sites and may be reviewed by the Sponsor as part of routine

safety monitoring. If clinically indicated, sites may obtain a white blood cell count and differential (including eosinophil count) at their local laboratory.

If unblinding by the investigator is necessary for patient management, the investigator will be able to break the treatment code by contacting the IxRS. Treatment codes should not be broken except in emergency situations. If the investigator wishes to know the identity of the study drug for any other reason, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding because of a serious adverse event).

As per health authority reporting requirements, Roche will break the treatment code for all unexpected serious adverse events (see Section 5.7) that are considered by the investigator to be related to study drug.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Lebrikizumab and Placebo

Study drug (lebrikizumab or placebo) will be supplied by the Sponsor in a prefilled syringe. During the 24-week placebo-controlled period, all patients will receive a single SC injection at each dosing visit via prefilled syringe. The prefilled syringe of active drug product will be supplied as sterile liquid formulations at a concentration of 125 mg/mL lebrikizumab. The formulation of the active drug also contains histidine acetate (20 mM), sucrose (60 mg/mL), polysorbate 20 (approximately 0.03%), and Sterile Water for Injection, USP, pH 5.4–6.0. The placebo will be supplied by the Sponsor as a sterile liquid formulation. Each prefilled syringe of placebo will contain Sterile Water for Injection with histidine acetate (20 mM), sucrose (75 mg/mL), and polysorbate 20 (approximately 0.03%), pH 5.4–6.0. Prefilled syringes of study drug and placebo should be refrigerated at 2°C–8°C and protected from excessive light and heat. Prefilled syringes should not be frozen, shaken, or stored at room temperature.

Prefilled Syringe Configuration

Prefilled syringes of study drug will be provided assembled with needle safety devices. Prefilled syringes will be labeled "Lebrikizumab or placebo."

Each prefilled syringe of active study drug contains 1 mL of sterile liquid at a concentration of 125 mg/mL lebrikizumab. The 1-mL volume injection of active drug corresponds to 125 mg of lebrikizumab. Each prefilled syringe of placebo contains 1 mL of sterile placebo formulation.

4.3.1.2 Inhaled Corticosteroid and Bronchodilator Therapy

Refer to the local prescribing information for the formulation, packaging, and handling of these medications.

4.3.2 Dosage, Administration, and Compliance

During the placebo-controlled period, patients will receive lebrikizumab 125 mg or placebo, administered by SC injection every 4 weeks (see Section 4.2 for details on treatment assignment). Patients will receive one injection per dosing visit from a prefilled syringe. Study drug will be supplied as follows:

- The lebrikizumab 125 mg arm is supported by one active prefilled syringe
- The placebo arm is supported by one placebo prefilled syringe

Each patient will receive a total of 6 doses of study drug during the placebo-controlled period.

4.3.2.1 Procedures for Study Drug Administration

Each prefilled syringe contains 1 mL of lebrikizumab or placebo for SC injection. Treatment with lebrikizumab or placebo will be by SC injection. Injections may be administered in the arm, thigh, or abdomen. Study sites will be asked to record each injection site and associated study drug kit number.

In the placebo-controlled period, patients will be monitored for a minimum of 1 hour after dosing. For additional details, refer to the schedule of assessments in Appendix 1.

No dosage modifications are permitted during the study. Guidelines for study drug discontinuation are provided in Section 4.6.

4.3.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (i.e., lebrikizumab and matching placebo) will be provided by the Sponsor. The study site will acknowledge receipt of IMPs, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Post-Trial Access to Lebrikizumab

Currently, the Sponsor does not have any plans to provide lebrikizumab or any other study treatments or interventions to patients who have completed the study. The Sponsor will evaluate whether to continue providing lebrikizumab in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following Web site:
http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf.

4.4 CONCOMITANT THERAPY

All medications used for the treatment of COPD within the 12 months prior to screening should be recorded on the COPD Targeted Concomitant Medications electronic Case Report Form (eCRF). All other medications (e.g., prescription medications) used by the patient within 6 months prior to the first screening visit should be recorded on the Concomitant Medications eCRF. A detailed history of prior exposure to monoclonal antibodies will be recorded. Vaccinations should also be entered on the Concomitant Medications eCRF.

4.4.1 Inhaled Bronchodilator and Corticosteroid Therapy

All patients will continue their COPD therapy as recommended in published COPD guidelines (GOLD 2015). Required COPD inhaler therapy for this study includes the following:

- Bronchodilator medication consisting of one of the following: LABA or LAMA

  Patients must be on an eligible bronchodilator medication for at least 6 months prior to Visit 1

  Patients must be on stable therapy for at least 4 weeks prior to Visit 1

  There must be no anticipated changes in bronchodilator medication during the study

  Patients may be on more than one bronchodilator

- ICS therapy

  Patients must be on ICS therapy for at least 6 months prior to Visit 1

  Patients must be on stable therapy for at least 4 weeks prior to Visit 1

  There must be no anticipated changes in ICS therapy during the study

Additional background COPD therapy is permitted during the trial (e.g., phosphodiesterase-4 inhibitors and theophylline) but should remain stable from the start of screening (Visit 1) through completion of the study. Theophylline dose may be adjusted as appropriate on the basis of theophylline levels.

From the start of screening (Visit 1) through completion of the study, the doses of bronchodilator medications and ICS should remain stable. If changes to the background COPD medications are unavoidable, the patient may be switched to another brand or

formulation that is equivalent to the medication that the patient was receiving at study entry. Any proposed changes should be discussed with the Medical Monitor. All changes to a patient's background medications should be documented in the COPD Targeted Concomitant Medications eCRF.

4.4.2 Rescue Therapy

It is expected that patients will be using short-acting anticholinergic and/or short-acting beta-agonist therapy for acute COPD symptoms per existing treatment guidelines. Combination inhalers (e.g., albuterol/ipratropium) are permitted. Short-acting bronchodilators must be administered via the patient's prescribed inhaler or nebulizer.

Patients will record the number of puffs or nebulized treatments of short-acting rescue therapy in the eDiary (see Section 4.5.1.17 for details). Any short-acting bronchodilator that is prescribed as COPD rescue medication over the course of the study should be documented in the COPD Targeted Concomitant Medications eCRF. Bronchodilator treatment administered during an urgent health care visit or hospitalization should also be recorded in the COPD Targeted Concomitant Medications eCRF, as appropriate.

4.4.3 Systemic Corticosteroid Use

Patients who require any systemic corticosteroids (oral, IV, or IM) during the 4 weeks prior to Visit 1 or during screening will not be eligible for the trial (see Section 4.1.2).

The use of oral, IV, or IM corticosteroids is permitted for acute patient management after randomization (Visit 2) and should be documented in the Concomitant Medications eCRF or the COPD Targeted Concomitant Medications eCRF, as appropriate. Corticosteroids used for treatment of COPD (e.g., an acute exacerbation event) should be documented on the COPD Targeted Concomitant Medications eCRF. Corticosteroids used to treat other medical conditions should be documented on the Concomitant Medications form. Documentation should include dose, total duration of therapy, and whether or not use is associated with a COPD exacerbation event.

4.4.4 Prohibited Therapy

Use of concomitant medications during the study is restricted per the instructions in Table 1. Patients should not be asked to alter their standard therapy in any way until the informed consent process is complete. The list of medications is not necessarily comprehensive and the investigator should consult the prescribing information for any concomitant medication. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed below.

Table 1 Concomitant Medication Restrictions

Medication	Restrictions [a]
ICS therapy	No changes in ICS therapy within 4 weeks prior to Visit 1 and throughout the study
Maintenance oral corticosteroids (daily or every other day)	Prohibited within 3 months prior to Visit 1 and throughout the study
LABAs LAMAs	No changes within 4 weeks prior to Visit 1 and throughout the study
Live attenuated vaccines	Prohibited within 4 weeks prior to Visit 1 and throughout the study
Immunomodulatory or immunosuppressive therapy (other than monoclonal antibodies or corticosteroids [see separate exclusion])	Prohibited within 3 months or 5 drug half-lives prior to Visit 1 (whichever is longer) and throughout the study
Immunomodulatory or immunosuppressive monoclonal antibodies	Prohibited within 6 months or 5 drug half-lives prior to Visit 1 (whichever is longer) and throughout the study
Anti–IL-13 (including lebrikizumab) or anti-IL-4/IL-13 [b]	Prohibited prior to and throughout the study
Any investigational drug not described above (including investigational use of a formulation of an approved drug)	Prohibited within 4 weeks or 5 drug half-lives prior to Visit 1 (whichever is longer) and throughout the study

ICS = inhaled corticosteroid; IL = interleukin; IM = intramuscular; IV = intravenous; LABA = long-acting β-agonist; LAMA = long-acting muscarinic agent; LTRA = leukotriene receptor antagonist; SC = subcutaneous.

[a] The Medical Monitor should be consulted in cases of uncertainty.

[b] Patients participating in a clinical trial that has not been unblinded should be assumed to have received the active drug.

4.4.4.1 Medication Use prior to Spirometry Measurements in the Clinic

Inhaled bronchodilator use is prohibited within a specified window prior to pre-bronchodilator spirometry measurements performed in the clinic, as follows:

- Twice-daily LABA and twice-daily LAMA: within 12 hours prior to spirometry
- Once-daily LABA and once-daily LAMA: within 24 hours prior to spirometry
- SABA/ipratropium: within 4 hours prior to spirometry

The patient should not be asked to alter his or her standard therapy in any way until the informed consent process is complete.

With the exception of Visit 1, a patient's visit must be rescheduled if the patient arrives for a study visit having used an inhaled bronchodilator within the time window defined above for each medication. To accommodate the rescheduled visit, the visit window

specified in the schedule of assessments (see Appendix 1) may be extended by a maximum of 4 calendar days.

For safety reasons, consideration should be given to omitting spirometry if a patient is having an acute COPD exacerbation event at the time of the scheduled study visit.

4.5 STUDY ASSESSMENTS

Please see Appendix 1 for the schedule of assessments performed during the study.

4.5.1 Description of Study Assessments

4.5.1.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.1.2 Medical History and Demographic Data

Demographic data will include age (date of birth), sex, and self-reported race/ethnicity.

Medical history will include clinically significant diseases and surgeries, smoking history, use of alcohol and drugs of abuse within the past year, and medication allergies. In particular, sites should record whether the patient has any history of anaphylaxis, cancer, cardiovascular disease, eosinophilic disease, inflammatory or autoimmune disease, and parasitic disease.

4.5.1.3 Vital Signs

Vital signs will include measurements of temperature, heart rate, systolic and diastolic blood pressure, and respiratory rate. It is recommended that blood pressure determinations are made using the same arm with the patient in a seated or semi-supine position for all study visits.

4.5.1.4 Height and Weight

Height and weight will be measured at visits according to the schedule of assessments in Appendix 1. Weight will be determined to the nearest 0.1 kg. For body weight measurements, the patient will wear street clothes without any shoes, outerwear, or accessories.

4.5.1.5 Physical Examinations

A complete physical examination should include, but is not necessarily limited to an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems.

Any abnormality identified during screening should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits, limited, symptom-directed physical examinations should be performed as per the Schedule of Assessments (Appendix 1). Changes from baseline abnormalities should be recorded in the source documents. New or worsened abnormalities should be recorded as adverse events on the Adverse Event eCRF, if appropriate.

4.5.1.6 Tobacco Use

At each study visit, the patient will be asked about their tobacco use. Any changes in tobacco use since Visit 1 will be recorded in the eCRF.

Patients may discontinue smoking at any time during the study.

4.5.1.7 Tobacco Cessation for Current Smokers

At Visit 1, patients who are current smokers will receive tobacco cessation counseling. *Current smokers are defined as those with history of cigarette smoking of ≥10 pack-years. Former smokers are defined as those who meet the definition of current smoker but have stopped smoking at least 6 months prior Visit 1.*

Patients will be reminded that smoking may accelerate the rate of lung function decline, worsen respiratory symptoms, increase the risk of lung cancer, and increase the risk for cardiovascular disease. Over time, tobacco cessation may lead to a slower rate of lung function decline, improve respiratory symptoms, and reduce the risk of cardiovascular disease. Patients may be referred to their primary care physician for further tobacco cessation support.

4.5.1.8 Acute COPD Exacerbations

The investigator will ask directed questions to assess whether the patient experienced any protocol-defined COPD exacerbations since the last study visit.

A moderate COPD exacerbation is defined as new or increased COPD symptoms (e.g., dyspnea, sputum volume, and sputum purulence) for at least 2 consecutive days that lead to treatment with systemic corticosteroids and/or antibiotics.

A severe COPD exacerbation is defined as new or increased COPD symptoms (e.g., dyspnea, sputum volume, and sputum purulence) for at least 2 consecutive days that lead to hospitalization.

Given that COPD exacerbations are the key secondary endpoint in this study, a dedicated eCRF will be used to record information regarding protocol-defined exacerbation events. A COPD exacerbation must also be reported as an adverse event (or serious adverse event as applicable) as per Section 5.2. Sites should update the

COPD Targeted Concomitant Medications eCRF with all medications used for treatment of the COPD exacerbation.

4.5.1.9 Urgent COPD-Related Health Care Utilization

At each study visit after randomization, the investigator will ask directed questions to assess whether the patient has required any urgent COPD-related health care since the last study visit. Urgent COPD-related health care utilization includes any hospitalizations, emergency department visits, and acute care visits (i.e., unplanned clinic visits). A dedicated eCRF will be used to record information regarding any COPD-related hospitalizations, emergency department visits, and/or acute care visits.

4.5.1.10 Patient-Reported Outcomes

PRO (SGRQ-C, EXACT, BDI/TDI, and mMRC) data will be collected to more fully characterize the clinical profile of lebrikizumab. The instruments will be translated as required in the local language.

The SGRQ-C, EXACT, and mMRC instruments will be completed in their entirety by the patient. The BDI/TDI will be administered by study staff to the patient. The mMRC will be collected on paper at the site. The SGRQ-C and BDI/TDI will be collected electronically at the site on a tablet device. Patients will complete the EXACT at home on a handheld eDiary for the seven days prior to each study visit. Electronic PRO (ePRO) devices and instructions for completing the PRO questionnaires will be provided to each patient by the investigator staff. To ensure instrument validity and that data standards meet health authority requirements, the site-based PRO instruments (the SGRQ-C, and BDI/TDI, and mMRC) should be administered at the investigational site prior to the completion of other non-PRO assessments and before the patient receives any disease-status information or study drug during that visit.

The PRO data will be collected and assessed at visits according to the schedule of assessments in Appendix 1. Copies of each questionnaire are provided in Appendix 2, Appendix 3, Appendix 4, and Appendix 5, which provide an example of the content; formatting may be adjusted for adaptation to the ePRO device.

St. George's Respiratory Questionnaire for COPD Patients

The impact of COPD on health and well-being, as measured by the SGRQ-C (Meguro et al. 2007), will be assessed by asking patients to recall their COPD-related experiences and to respond to 40 questions included within three domains: symptoms (7 items), activity (13 items), and impacts (20 items). The SGRQ-C does not specify a recall period with the exception of the item that assesses chest trouble. This item has a recall period of the past year. Lower scores of the SGRQ-C indicate better health-related quality of life. A copy of the assessment is provided in Appendix 2.

Exacerbations of Chronic Pulmonary Disease Tool

The EXACT is a daily diary that assesses COPD exacerbations (Leidy et al. 2010). The 14-item questionnaire contains four domains: breathlessness (five items), cough and sputum (three items), chest symptoms (three items), and additional attributes (three items). The EXACT has a recall period of today. Patients will complete the EXACT at home for the seven days prior to each study visit except for Week 1 (Visit 3). A copy of the assessment is provided in Appendix 3.

Baseline Dyspnea Index/Transition Dyspnea Index

The BDI and TDI are each three-item questionnaires that measure breathlessness in three domains: functional impairment, magnitude of task, and magnitude of effort (Mahler et al. 1984). Both instruments are interviewer administered by site staff. The BDI is administered at the site at the baseline visit. The BDI score ranges from 0 (very severe impairment) to 4 (no impairment) for each domain and are summed to determine the BDI total score (0–12). The recall period of the BDI is present time. The TDI is administered at the site during the treatment phase per the schedule of assessments (see Appendix 1). The TDI score ranges from -3 (major deterioration) to $+3$ (major improvement) for each domain. The sum of all domains yields the TDI total score (-9 to $+9$). The recall period of the TDI is since the baseline visit (Randomization). Copies of the instruments are available in Appendix 4.

Modified Medical Research Council Dyspnea Scale

The mMRC scale assesses dyspnea (Bestall et al. 1999). Patients rate how much their breathlessness impacts their mobility. The mMRC is a five-item scale. Zero represents the least impairment due to dyspnea and four indicates greatest impairment due to dyspnea. There is no recall period for the mMRC. The mMRC is administered at the site on paper. The mMRC is completed at Visit 1 and Visit 2 *and* also completed throughout the treatment *and follow-up* period as a component of the BODE index, as specified in the schedule of assessments (see Appendix 1). A copy of the scale is available in Appendix 5.

4.5.1.11 Electrocardiograms

Single 12-lead ECG recordings will be obtained at Visit 1 (screening), Visit 2 (Randomization), at Week 24, and at Week 36. Standard procedures for obtaining high-quality ECGs should be followed.

ECGs for each patient should be obtained from the same machine whenever possible. To minimize variability, it is important that patients be in a resting position for ≥ 10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to any scheduled study procedures (e.g., blood draws, study drug administration).

Machine-generated ECG intervals will be entered in the eCRF. For safety monitoring purposes, the presence of abnormalities on any of the ECGs will be documented on the eCRF. Any ECG changes that are associated with symptoms or lead to a change in study treatment, concomitant treatment, or discontinuation from study treatment, must be reported as an adverse event on the adverse event eCRF (see Section 5.2.1). The investigator or designee must review, sign, and date all ECG tracings. Paper copies will be kept as part of the patient's permanent study file at the site. De-identified copies of all ECGs will be electronically transmitted or mailed for storage centrally at a designated contract research organization (CRO).

4.5.1.12 Spirometry

Spirometry, including the procedure for bronchodilator testing, will be conducted as per the study pulmonary function testing manual, which is based on the American Thoracic Society/European Respiratory Society (ATS/ERS) Consensus Statement "Standardisation of Spirometry" (Miller et al. 2005). The manual will include information on equipment, procedures, patient instructions, and precautions.

Measurement of spirometry will be performed on a computerized spirometry system, Vitalograph® 6600 COMPACT™ (Vitalograph; Ennis, Ireland) configured to the requirements of the study and in accordance with guidelines published by the ATS/ERS (Miller et al. 2005).

Pre-bronchodilator spirometry and post-bronchodilator spirometry will be performed according to the schedule of assessments in Appendix 1. For safety reasons, consideration should be given to omitting spirometry if a patient is having an acute COPD exacerbation event at the time of the scheduled study visit.

Spirometric measures will include FEV_1 and FVC (volume in liters) and flow–volume and volume–time curves will be generated. The percentage of predicted FEV_1 and percentage of predicted FVC will be derived from these volume measurements using the equations derived from the third National Health and Nutrition Examinations Survey (Hankinson et al. 1999). The acceptability of the data, including the graphic representations of the maneuvers, will be determined by blinded over-readers. Calculations for the reproducibility of the acceptable maneuvers will be programmed.

Inhaled bronchodilator therapies that may affect spirometry must be withheld until pre-bronchodilator spirometry measurements are completed. Patients must be made aware that inhaled bronchodilator use is prohibited within a specified window prior to each clinic visit, with the exception of Visit 1, as follows:

- Twice-daily LABA and twice-daily LAMA: within 12 hours prior to spirometry
- Once-daily LABA and once-daily LAMA: within 24 hours prior to spirometry
- SABA/ipratropium: within 4 hours prior to spirometry

With the exception of Visit 1, a patient's visit must be rescheduled if the patient arrives for a study visit having used an inhaled bronchodilator within the window defined above for each medication. To accommodate the rescheduled visit, the visit window specified in the schedule of assessments (see Appendix 1) may be extended by a maximum of 4 calendar days.

A repeat Visit 1 spirometry session may be performed if the Visit 1 spirometry is rejected by the over-reader. Visit 1 spirometry is the only spirometry session that may be repeated (see the pulmonary function testing manual for details).

4.5.1.13 Chest X-Rays

A chest X-ray must be performed during screening (between Visit 1 and Visit 2) unless a chest X-ray or CT scan has been *performed* within *6* months prior to Visit 1 and *the scan or radiologist report* is available for review by the investigator. The X-ray may be performed locally but *the X-ray or radiologist report* must be reviewed by the investigator prior to randomization at Visit 2. If a chest X-ray or CT scan is not available in the *6* months preceding Visit 1 or a chest X-ray cannot be completed during screening, the patient will not be eligible for the study.

4.5.1.14 Six-Minute Walk Test

The 6MWT will be conducted as per the study 6MWT Procedural Manual that is based on the 2002 ATS guidelines for the 6MWT (ATS Statement 2002).

For safety reasons, all patients should be clinically stable prior to performing any study-related 6MWT.

Supplemental oxygen flow rate will be recorded before every 6MWT. Heart rate, oxygen saturation (SpO_2), and the Borg Category Ratio 10 (CR10) Scale® will be recorded immediately before and after the procedure. The Borg CR10 Scale is a one-item assessment that can be used to measure a variety of perceptions and experiences (i.e., perceived exertion, chest pain, dyspnea, and fatigue) (Borg and Borg 2010). The Borg CR10 Scale ranges from 0 (Nothing at all) to 10 (Absolute maximum/Highest possible). For more information, see Appendix 6 and Appendix 7.

4.5.1.15 BODE Index

The BODE index is a composite score of other assessments collected in the study. Body mass index (B), obstruction (O) as measured by FEV_1, dyspnea (D) as measured by the mMRC scale, and exercise endurance (E) as measured by the 6MWT will be assessed as described under the separate sections for each assessment. The standard scoring system will be followed (Celli et al. 2004).

4.5.1.16 Laboratory and Biomarker Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Urine pregnancy test for all women of childbearing potential, including those who have had a tubal ligation (see Appendix 8). Urine pregnancy tests will be performed prior to administration of study drug and at other specified visits. If a local urine pregnancy test shows a positive result, study drug will not be administered that day. The result must be confirmed by a serum pregnancy test (conducted by the central laboratory). Refer to Section 5.4.3.1 for management of a patient with a confirmed pregnancy.

Samples for the following laboratory tests will be sent to one or several central laboratories for analysis:

- Serum pregnancy tests will be performed at screening for all women of childbearing potential, including those who have had tubal ligation (see Appendix 8). Urine pregnancy tests will be performed prior to administration of study drug at subsequent visits and at other specified visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test (conducted by the central laboratory) and study drug will not be administered that day. Refer to Section 5.4.3.1 for management of a patient with a confirmed pregnancy.
- Hematology (hemoglobin, hematocrit, platelet count, WBC count, percent and absolute differential count [neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells])
- Serum chemistry (sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase, creatine phosphokinase, uric acid)
- Urinalysis (protein, blood, glucose, and microscopic [RBC, WBC, casts, and crystals])

Samples for the following laboratory tests will be sent to the Sponsor or a designee for analysis:

- Serum for IL-13– and COPD–related biomarkers including but not limited to periostin, IgE, CCL-13, CCL-17, and CCL-18
- *Plasma for IL-13- and COPD-related biomarkers, including but not limited to plasma PD samples for research purposes, including fibrinogen*
- Immunogenicity assessment: serum samples will be assayed for the presence of antibodies against lebrikizumab using validated bridge immunoassays. Serum samples may also be assayed for the presence of antibodies against PLBL2. Samples that screen positive will be further characterized by immunodepletion and titer.
- PK assessments: lebrikizumab concentrations in serum will be measured using a validated quantitative immunoassay

4.5.1.17 eDiary Assessments Completed by the Patient at Home

Patients will be provided with a handheld diary device at Visit 1. This device will be used for eDiary recording of background COPD medication use, rescue medication use, and the completion of the EXACT during the study. Data from the eDiary will transmit automatically on a daily basis. The information recorded on the daily diary will be reviewed at each study visit. At Visit 1, all patients will receive hands-on training on the use of the eDiary, including review of the user guide. Patients will also be instructed to contact the site promptly if they have any questions about the use of the device during screening or at any time during the study.

Adherence with Inhaled Corticosteroids and Bronchodilator Therapy

At Visit 1, patients will be instructed on the proper technique recommended for administration of their ICS therapy and inhaled bronchodilator therapy.

Patients will be instructed to record their background COPD medication use daily in the eDiary.

Short-Acting Rescue Medication

Patients will be instructed to record their rescue medication use daily in the eDiary. Each daily recording will capture rescue medication use for the period since the last recording.

Exacerbations of Chronic Pulmonary Disease Tool

Patients will complete the EXACT on the eDiary. Patients will answer the 14-item questionnaire at home for the seven days prior to each study visit.

4.5.1.18 Optional Samples for Roche Clinical Repository

Overview of the Roche Clinical Repository

The Roche Clinical Repository (RCR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition

- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol (Section 4.5.1.18) will not be applicable at that site.

Sample Collection

The following samples will be collected for research on dynamic (non-inherited) biomarkers:

- Residual serum samples from PD, PK, and antibody testing for research purposes, including, but not limited to, research on biomarkers related to IL-13, COPD, COPD-related diseases, or other respiratory diseases
- Whole blood PAXgene samples for RNA extraction for research purposes, including but not limited to research on biomarkers related to IL-13, COPD, COPD-related diseases, or other respiratory diseases

The following samples will be collected for research on genetic (inherited) biomarkers:

- Whole blood samples for DNA extraction for research purposes, including, but not limited to, research on biomarkers related to IL-13, COPD, COPD-related diseases, or other respiratory diseases

The purpose of collecting optional RNA samples is to increase the understanding of the impact of COPD with and without lebrikizumab treatment on peripheral blood gene expression. These studies may help identify biomarkers to increase understanding of disease severity, disease progression, and clinical heterogeneity of the disease and possible drug response.

The purpose of collecting the optional DNA sample is to study genetic determinants that may predict response to lebrikizumab and other therapies typically used in treatment of COPD, as well as to understand the relationship between heritable factors and clinical features of COPD. Single nucleotide polymorphisms (SNPs) in the periostin gene can also be examined to determine the effect of SNPs on expression of periostin mRNA as well as protein levels in peripheral blood.

For all samples, dates of consent should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC–approved ICF and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens and associated data. Upon receipt by the RCR, each specimen is "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Patient medical information associated with RCR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RCR data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. Patients will be

told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RCR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate by completing the RCR Research Sample Informed Consent eCRF.

In the event of an RCR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RCR research.

Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study WB29804 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study WB29804.

Monitoring and Oversight

RCR specimens will be tracked in a manner consistent with Good Clinical Practice (GCP) by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

4.5.2 Timing of Study Assessments

4.5.2.1 Screening and Pretreatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. ICFs for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site. Patients then commence a screening period of at least 14 days' duration that includes the first screening visit (Visit 1) as well as a final assessment of eligibility prior to randomization at Visit 2 (Randomization, Day 1). All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all

patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Patients may be eligible for rescreening for selected reasons up to two additional times*, with all inclusion and exclusion criteria being re-assessed*.

At Visit 1, all patients will receive hands-on training in use of the eDiary and tablet, including review of the user guide. Patients will also be instructed to contact the site promptly if they have any questions about the use of the device during screening or at any time during the study. Adherence to background COPD medication treatment for the weeks between Visits 1 and 2 will be downloaded from the eDiary, and adherence during the screening period will be calculated automatically. Patients will also record their use of rescue medication in the eDiary.

At Visit 1, patients who meet the protocol definition of current smoker will receive tobacco cessation counseling (see Section 4.5.1.7 for more details).

A chest X-ray must be performed during screening unless a chest X-ray or CT scan has been *performed* within *6* months prior to Visit 1 and *the scan or radiologist report* is available for review by the investigator. The X-ray may be performed locally but *the scan or radiologist report* must be reviewed by the investigator prior to randomization at Visit 2. If a chest X-ray (or CT scan) is not available in the *6* months preceding Visit 1 and cannot be completed during screening, the patient will not be eligible for the study.

Spirometry will be performed at Visits 1 and 2. Patients must demonstrate a post-bronchodilator FEV_1/FVC ratio <0.70 and FEV_1 of $<80\%$ predicted at Visit 1 or Visit 2 to be eligible for the trial. A repeat Visit 1 spirometry session may be performed if the Visit 1 spirometry is not accepted by the over-reader. Visit 1 spirometry is the only spirometry session that may be repeated (see the pulmonary function testing manual for details).

At Visit 2, the first assessment will be review of adherence data. Patients who are adherent with their background COPD therapy for $\geq 70\%$ of days during the screening period (Visits 1–2) will continue with planned assessments at Visit 2. Patients who do not meet the adherence eligibility criterion should not proceed with the remaining Visit 2 study assessments on that day.

Patients not adherent with their background COPD medications from Visits 1 to 2, as evidenced by $<70\%$ adherence during the screening period, will not be eligible for the study. However, the screening period may be extended by 1 week for additional adherence monitoring in the case of device malfunction or extenuating patient circumstances. *In such cases, the Sponsor or designee should be contacted to review the case prior to extending the screening period. If the screening period is extended*, the

adherence calculation will be based on the number of days the patient was adherent to baseline therapy when the device was used and functioning properly.

Please see Appendix 1 for the schedule of screening and pretreatment assessments.

4.5.2.2 Assessments during Treatment

The 24-week placebo-controlled period begins *after* randomization *and* first dose of study drug*, once all study procedures and assessments have been completed*. Patients who complete study drug dosing visits during the 24-week placebo-controlled period will enter the safety follow-up period.

All assessments must be performed on the day of the specified visit unless a time window is specified in the schedule of assessments (see Appendix 1). The order of assessments must conform to the following requirements:

- The SGRQ-C, BDI/TDI, and mMRC must be administered prior to the completion of other non-PRO assessments and before the patient receives any disease-status information or study drug during that visit
- ECGs must be performed prior to any scheduled spirometry measurements or blood draws
- For female patients of childbearing potential, urine pregnancy test results must be reviewed and confirmed to be negative before study drug administration
- Study drug must be administered after all other assessments have been completed

Please see Appendix 1 for the schedule of assessments performed during the study.

4.5.2.3 Assessments during Safety Follow-Up and at Study Completion

All patients who complete study drug dosing during the placebo-controlled period will be followed for safety for 16 weeks (>4 half-lives of the drug) after the last dose of study drug. This includes the last 4 weeks in the placebo-controlled period and 12 weeks in the safety follow-up period. The first safety follow-up visit (Visit 10) will take place approximately 4 weeks after the last visit of the placebo-controlled period. The study completion visit is the Week 36 visit (Visit 11) in the safety follow-up period.

Patients who discontinue study drug early during the placebo controlled period may be followed for more than 16 weeks after the last dose (see Section 4.6.2 for details of follow-up of patients who discontinue study drug early).

Please see Appendix 1 for the schedule of assessments performed during the safety follow-up period.

4.5.2.4 Assessments at Early Termination

Patients who withdraw from the study (regardless of the reason) and refuse safety follow-up should complete an early termination (ET) visit. The ET visit should take place

4 weeks (±7 days) after the last dose of study drug. Patients who wish to withdraw from the study during the safety follow-up should also complete an ET visit. Please see Section 4.6.1 for details.

Please see Appendix 1 for the schedule of assessments performed at the ET visit.

4.5.2.5 Follow-Up Assessments

After the study completion/early termination visit, adverse events should be followed as outlined in Section 5.5 and Section 5.6.

4.5.2.6 Assessments at Unscheduled Visits

Please see Appendix 1 for assessments that are required to be performed in case of an unscheduled visit. An unscheduled visit may occur at any time during the study.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 Study Treatment Discontinuation

Patients must discontinue study drug if they experience any of the following:

- Pregnancy
- Anaphylactic, anaphylactoid, or serious hypersensitivity reaction associated with IMP
- Malignancy (including basal or squamous cell carcinoma of the skin or carcinoma in situ)

Patients who discontinue study drug prematurely during the placebo-controlled period should be asked to continue with all scheduled study assessments in the placebo-controlled period and then continue to the safety follow-up period. Patients who are unable or unwilling to complete the study assessments in the placebo-controlled period should complete a DT visit and then enter the safety follow-up period.

The primary reason for premature study drug discontinuation should be documented on the appropriate eCRF. Patients who discontinue study drug prematurely will not be replaced.

All patients who discontinue study drug early should be followed for safety for at least 16 weeks after the last dose of study drug. This may include the 4 weeks after the final dose during the study treatment period and a 12-week safety follow-up period.

4.6.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory
- Data recording is inaccurate or incomplete

The Sponsor will notify the investigator if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP)
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Lebrikizumab is not an approved drug and is currently in clinical development $also$ for asthma, atopic dermatitis, and idiopathic pulmonary fibrosis. Thus, the entire safety profile of lebrikizumab is not fully characterized at this time.

The safety plan for this study is designed to ensure patient safety and will include specific eligibility criteria and specific pharmacovigilance monitoring assessments as detailed below.

5.1.1 Internal Monitoring Committee

An IMC will be used to carefully review the accumulating safety data.

The IMC will consist of Sponsor representatives from the following functions: Clinical Science, Drug Safety, *and* Biostatistics. The IMC members will be external to the Sponsor's Study Management Team, except for the Biostatistics representative.

The IMC will regularly monitor the safety of the patients in the study. Details on the IMC will be documented in an IMC agreement.

5.1.2 Events to be Monitored for Lebrikizumab

Based on safety data to date, the theoretical risks associated specifically with IL-13 inhibition, and the risks associated with biologic agents in general, the following potential adverse events have been identified as events to be monitored (EtM) for lebrikizumab:

- Local injection-site reactions
- Infections
- Anaphylactic, anaphylactoid, and hypersensitivity reactions
- Malignancies

Collection of information about these EtM allows for better evaluation and understanding of any potential safety risk to patients (refer to the Lebrikizumab Investigator's Brochure for more details).

Anaphylactic, anaphylactoid, or other hypersensitivity reactions and malignancy events are also considered to be adverse events of special interest (AESIs) with a requirement for expedited reporting of these events from sites to the Sponsor (see Section 5.2.3).

The following risk mitigation measures apply to patients receiving study drug:

- Adherence to the planned dose regimen of study drug is required unless dosing is held for safety reasons
- If study drug is withheld because of toxicity, all other study assessments for that visit should be performed as per the study schedule

5.1.2.1 Local Injection-Site Reactions

A local injection-site reaction is any local reaction occurring at the site of injection following study drug administration.

In completed Phase II clinical trials with lebrikizumab, injection-site reactions were reported in a greater proportion of lebrikizumab-treated patients than placebo-treated patients. These events were all non-serious and, in most cases, did not require treatment.

Local injection-site reactions, including but not limited to erythema, induration, and pain, should be reported as an adverse event. The event term should be recorded in the dedicated Injection Reactions eCRF as the symptom, preceded or followed by "injection

site" (e.g., "injection-site erythema" or "erythema at injection site"). If needed, injection-site reactions should be treated and any treatments should be reported on the eCRF.

Injection-site reactions will be monitored closely, with site training in the recognition and reporting of events. Detailed information regarding injection-site reactions that occur during the study will be collected, regardless of seriousness criteria.

5.1.2.2 Anaphylactic, Anaphylactoid, and Hypersensitivity Reactions

In completed Phase I/II clinical trials of lebrikizumab, no anaphylactic, anaphylactoid, or serious hypersensitivity reactions were observed; however, anaphylaxis and hypersensitivity reactions are considered a potential risk with all biologic medications, including lebrikizumab.

Patients with a history of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the lebrikizumab injection are excluded from study participation.

Signs of a possible anaphylactic, anaphylactoid, or hypersensitivity reaction include but are not limited to the following:

- Fever, chills, pruritus, urticaria, angioedema, and skin rash
- Cardiopulmonary reactions, including chest pain, dyspnea, hypotension, or hypertension
- Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

Investigators and healthcare professionals administering lebrikizumab should be trained to recognize and manage the signs and symptoms of a potential anaphylactic, anaphylactoid, or hypersensitivity reaction and should be familiar with Sampson's criteria for defining anaphylaxis (Sampson et al. 2006; see Appendix 9). Investigators and healthcare professionals should also be trained to accurately and appropriately report these events immediately to the Sponsor as AESIs and as serious adverse events, if appropriate (see Section 5.2). Site staff should also instruct patients on how to recognize the symptoms of any anaphylactic, anaphylactoid, or hypersensitivity reaction and to contact a health care provider or seek emergency care in case of any such symptoms. Patients will need to be clinically stable prior to receiving each dose of study drug as assessed by clinical evaluations, including vital signs measurements.

Throughout the study, patients will be monitored for a minimum of 1 hour after the injection is administered at each dosing visit.

Anaphylactic, anaphylactoid, or hypersensitivity reactions should be reported immediately to the Sponsor as AESIs and as serious adverse events if appropriate. If a patient experiences a suspected and/or non-serious hypersensitivity reaction, the case should be discussed with the Medical Monitor prior to continuing dosing. If a patient has

signs or symptoms of an anaphylactic, anaphylactoid, or serious hypersensitivity reaction associated with IMP, administration of the study drug must be discontinued permanently (refer to Appendix 9 for suggested clinical criteria for diagnosis of anaphylaxis). The patient should be treated according to the standard of care for management of anaphylaxis or an anaphylactoid or hypersensitivity reaction. The patient must discontinue study drug but, whenever possible, should continue to be followed in the study (see Section 4.6.2). Blood samples for antibody testing and lebrikizumab concentration should be obtained at the time of the event whenever possible, and a blood sample for antibody testing and lebrikizumab concentration should be obtained at the first follow-up visit after the event (see Appendix 1).

Detailed information regarding anaphylactic, anaphylactoid, or hypersensitivity reactions that occur during the study will be collected, regardless of seriousness.

5.1.2.3 Infections

Although parasitic infections have not been observed clinically to date, experimental animal models suggest that IL-13 plays a role in the immune response to gastrointestinal nematodes. IL-13 may also play a role in the progression from infection to the development of clinical disease with parasites such as *Leishmania* and intracellular pathogens, such as *L. monocytogenes*. Patients and study investigators will be advised of this possibility, particularly if the patient has a relevant travel history (for *Leishmania* or other parasites). Patients should be instructed in appropriate food preparation and travel precautions and be made aware of the need to seek medical attention for possible symptoms of *L. monocytogenes* infection.

Patients with an active parasitic infection or *L. monocytogenes* infection within the 6 months prior to screening or during screening will be excluded from study participation.

The role of IL-13 in other infections is less clear. In the completed Phase II clinical studies of lebrikizumab, infections have not been associated with lebrikizumab.

Patients with a history of active tuberculosis requiring treatment within the 12 months prior to screening will be excluded from study participation. Patients who have completed treatment for tuberculosis at least 12 months prior to Visit 1 and have no evidence of recurrent disease are permitted.

In addition, patients *with any* infection *that results in* hospitalization *and/*or treatment with oral*, IV, or IM* antibiotics within *4* weeks prior to screening *or Visit 1* will be excluded.

Patients with an episode of infection of the upper or lower respiratory tract within 4 weeks prior to Visit 1 or during screening are excluded, even if the infection did not require antibiotics.

All infections that occur during the study, including non-serious infections such as viral upper respiratory infections, will be monitored. Detailed information regarding parasitic or other infections that occur during the study will be collected, regardless of whether the events are serious (see Section 5.2.2) or non-serious (see Section 5.2.3).

Given that blockade of the effector function of IL-13 constitutes immune modulation, patients will be excluded if they are receiving other immunomodulatory therapies (because of the uncertainty of the combined effect of lebrikizumab with such therapies) or if they have a known immunodeficiency, including but not limited to HIV infection (please see Section 4.1.2 for additional details regarding exclusion criteria).

5.1.2.4 Malignancies

The impact of IL-13 inhibition on the development of malignancies is not known. All patients with a known current malignancy or who are undergoing workup for a potential malignancy will be excluded from the study. Study drug must be discontinued in patients who develop malignancies (including basal or squamous cell carcinoma of the skin or carcinoma in situ).

Malignancies should be reported immediately to the Sponsor as AESIs, and as serious adverse events if appropriate. Detailed information regarding any malignancies that occur during the study will be collected, regardless of whether the events are serious (see Section 5.2.2) or non-serious (see Section 5.2.3).

5.1.3 Other Events: Immunogenicity

Antibody response to lebrikizumab will be assessed and antibody response to PLBL2 may be assessed (see Section 4.5.1.16). To assess for the potential development of immunogenicity, blood samples for antibody testing will be obtained (see Appendix 1). To ensure that an accurate assessment of immunogenicity is obtained, a final blood sample for antibody testing will be obtained from all patients at the final visit (study completion or early discontinuation). Samples will be stored appropriately for further evaluation as needed.

Antibodies to lebrikizumab: As with administration of any exogenous protein, a potential exists for the development of antibodies to lebrikizumab or to other proteins contained in the drug material, which could have neutralizing and/or sensitizing effects resulting in reduced efficacy and/or safety. Data obtained to date in completed clinical trials do not suggest an increased incidence of ATAs to lebrikizumab. In the few patients with positive post-treatment anti-therapeutic antibody (ATA) to lebrikizumab in completed trials, no clinically detectable response as assessed by PK, efficacy, or safety data was seen.

Antibodies to PLBL2: A positive antibody response to PLBL2 has been observed in patients treated with the previous clinical trial material containing higher levels of PLB2. The clinical significance of the antibody response is not known, and no clinically

important safety signals have been identified in completed studies. Following nonclinical and clinical safety assessment, manufacturing process changes have been implemented to generate clinical material with levels of PLBL2 reduced to acceptable levels. This new clinical material will be used in this study.

Refer to the Lebrikizumab Investigator's Brochure for more detail.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)

- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death). This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

The investigator is required to report all adverse events of special interest to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- Adverse events of special interest for general drug development:

  Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)

  Suspected transmission of an infectious agent by the study drug. Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient

exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

- Adverse events of special interest for lebrikizumab (see Section 5.1.2 for further information):

  Anaphylaxis, anaphylactoid, and hypersensitivity reactions

  Malignancies

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4–5.6. The investigator is also responsible for reporting medical device complaints (see Section 5.4.4).

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., blood draws) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 16 weeks after the last dose of study drug. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

Table 2 provides guidance for assessing adverse event severity.

Table 2 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 *Injection-Site Reactions*

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug injection should be captured as a diagnosis (e.g., "injection-site reaction" or "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Injection Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Injection Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.5) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event (see Section 5.2.2) or a non-serious adverse event of special interest (see Section 5.2.3).

5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of COPD.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the

cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

If the death is attributed to progression of COPD, then "COPD progression" should be recorded on the Adverse Event eCRF.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of COPD

Medical occurrences or symptoms of deterioration that are anticipated as part of COPD should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of COPD on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "exacerbation of COPD," "worsening of COPD").

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization *(i.e., in-patient admission to a hospital) or prolonged* hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be adverse events:

- *Hospitalization for respite care*
- *Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)*
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not *experienced* an adverse event

The following hospitalization scenario is not considered to be a serious adverse event but should be reported as an adverse event instead:

- *Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours*

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, site staff will alert the investigator, who will determine if the criteria for an adverse event have been met and will document the outcome of this assessment in the patient's medical record per site practice. If the event meets the criteria for an adverse event, it will be reported on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery

- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor: [redacted], *M.D., ScD.* (primary)

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

Medical Monitor: [redacted], M.D. (secondary)

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and e-mailing the form with use of the fax number or e-mail address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 16 weeks after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours

after learning of the event), either by faxing or by scanning and e-mailing the form with use of the fax number or e-mail address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within *18* weeks after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Roche Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

In the event that the EDC system is unavailable, the Clinical Trial Pregnancy Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and e-mailing the form using the fax number or e-mail address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3.2 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.4 Reporting Requirements for Medical Device Complaints

In this study, the prefilled syringe is considered a medical device. The investigator must report all medical device complaints to the Sponsor. The investigator should document

as much information as possible on the IMP Deviation Form, including the product batch number, and forward the form to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; refer to the pharmacy manual for further details). If the medical device results in an adverse event to the study patient, the event must be reported on the Adverse Event eCRF and submitted through the EDC system. If the event is serious, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.4.2.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 16 weeks after the last dose of study drug), if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and e-mailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form with use of the fax number or e-mail address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Lebrikizumab Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The primary and secondary efficacy analyses will be based on a modified intent-to-treat (mITT) approach. *The definition of mITT is a*ll patients randomized who received at least one dose of study drug will be included in the analysis, with patients grouped according to the treatment assigned at randomization.

The primary analysis will be performed after all patients have either completed the Week 12 visit or discontinued from the placebo-controlled period prematurely. The *final* analysis of data will be performed when all patients have either completed the Week *36* visit or discontinued from the placebo-controlled period prematurely, and all data from the placebo-controlled period are in the database and have been cleaned and verified.

Aggregate results of data from the 24-week placebo-controlled period may be reported to the public before completion of the study. However, patients and study site personnel will remain blinded to the individual treatment assignment until after the study is completed (after all patients have either completed the safety follow-up period or discontinued early from the study), the database is locked, and the study analyses are final.

All primary and secondary hypotheses tests will be two-sided. The focus of the trial is to generate hypotheses to be confirmed in future Phase III trials; therefore, there will be no type-1 error control. Detailed specifications of the statistical methods will be documented prior to database lock. All treatment group comparisons will be made within each of the biomarker-high (baseline blood eosinophils $\geq$300 cells/μL *or* baseline serum

periostin ≥50 ng/mL) and biomarker-low (baseline blood eosinophils <300 cells/μL *and* baseline serum periostin <50 ng/mL) subgroups. *Other ranges might be explored.*

6.1 DETERMINATION OF SAMPLE SIZE

The purpose of this study is to evaluate the efficacy of lebrikizumab compared with placebo in improving lung function, as measured by the change from baseline of pre-bronchodilator FEV_1 in biomarker-high COPD patients.

The study will enroll approximately 300 patients. Patients will be randomized in a 1:1 ratio to receive treatment with either lebrikizumab 125 mg or placebo every 4 weeks, in addition to standard-of-care COPD medications. The sample size of 150 patients per arm provides at least 80% power to detect a 77 mL (approximately 5.7 percent change from baseline [Dransfield et al. 2014]) difference in pre-bronchodilator FEV_1 change from baseline at Week*s 12 and* 24 between treatment groups among patients within the biomarker-high subgroup (75 biomarker-high patients in the lebrikizumab arm compared with 75 biomarker-high patients in the placebo arm) under the following assumptions:

- The absolute change from baseline at Week *12* in pre-bronchodilator FEV_1 is normally distributed with a standard deviation of 210 mL
- Two-sided alpha is 0.20
- Prevalence of the biomarker-high subgroup is at least 50% of the sample
- Drop-out rate at Week *12* is 10%, leading to a 10% loss of information

The assumed standard deviation of 210 mL was obtained by taking the square root of the sample-size weighted average of pooled population variance estimates as reported on clinicaltrials.gov. These COPD trials were selected because of the similarity of inclusion/exclusion criteria to the current trial.

Table 3 Sources of Statistical Assumptions used in Determining Power in Analysis of FEV_1 *at 24 Weeks*

SD (mL)	Sample Size	ΔFEV_{1Treat}-$\Delta FEV_{1Control}$	NCT Number(s)	Active Drug	Control Drug
287	342	117	NCT00784550	ADVAIR + SPIRIVA	Placebo + PIRIVA
192	933	49	NCT00313209	Roflumilast + salmeterol	Placebo + salmeterol
229	743	80	NCT00424268	Roflumilast + tiotropium	Placebo + tiotropium
155	626	71	NCT01313494	Roflumilast + Salbutamol	Placebo + salbutamol

In addition, the sample size provides at least 70% power to detect a 50% reduction in annual COPD exacerbation rate in the lebrikizumab group compared with placebo within the biomarker-high subgroup under the following assumptions:

- The number of COPD exacerbations experienced by a given patient during the 24-week placebo-controlled period follows a negative binomial distribution with a shape parameter of 1.3 and a placebo event rate of 0.8 exacerbations/52 weeks, leading to an overdispersion factor of 2.0 (Friede and Schmidli 2010).
- Two-sided alpha is 0.20
- Prevalence of the biomarker high subgroup is at least 50% of the sample
- Drop-out rate is uniform over the course of the study and at Week 24 is 10%, leading to a 5% loss of information

The placebo event rate was taken as the low end of the range from the studies listed in the table below. The shape parameter was calculated as the sample size weighted average shape parameter reported in the studies below.

Table 4 Sources of Statistical Assumptions used in Determining Power in Analysis of Exacerbations

Total Sample Size	Shape	Ref. Group Sample Size	Ref. Annual Events/ 52 wks	NCT Number(s)	Active Drug	Reference Drug
3439	1.0	1721	0.8	NCT00845728	Indacaterol	Tiotropium
2747	0.7	1845	1.1 [a]	NCT00292552	Obs. NA	Obs. NA
3261	1.7	818	1.0	NCT01009463, NCT01017952	Fluticasone Furoate/ GW642444	GW642444
3091	1.7	1544	1.4	NCT00297102, NCT00297115	roflumilast	placebo
1465	0.5	361	1.3	(Keene et al. 2007)	salmeterol/ fluticasone	placebo

NA = not applicable; wks = weeks.

[a] Weighted average of GOLD Stage 2 and 3.

Statistical power for both change in pre-bronchodilator FEV_1 and exacerbations was calculated using East 6.2® Cytel Inc. 2013. The study is not designed to detect treatment efficacy differences between the biomarker-high and biomarker-low subgroups (test of biomarker by treatment interaction effect).

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients randomized will be tabulated by study site, treatment arm, and biomarker subgroups. Patient disposition (the number of patients randomized, treated,

and completing each study period) will be tabulated by treatment arm and biomarker group. Premature study drug discontinuation and study discontinuation, as well as reasons for protocol deviations will be summarized.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics, such as age, sex, race/ethnicity, blood eosinophil level, serum periostin level, smoking status, history of COPD exacerbations within the last 12 months, pulmonary function, health status (as measured by the SGRQ-C), comorbid illness, baseline COPD medications (double vs. triple therapy), bronchodilator reversibility (present, absent), geographical region *(American Continent, ROW),* and participation in the CT substudy (yes, no) will be summarized for all randomized patients by treatment arm and biomarker subgroup using descriptive statistics (e.g., mean, standard deviation, minimum and maximum). Exposure to study drug (number of study drug treatments and duration of treatment) will be summarized by treatment arm, biomarker subgroup, and study period.

6.4 EFFICACY ANALYSES

*T*he primary efficacy endpoint and each secondary efficacy endpoint will each be performed separately within a*n appropriate regression* model (one per endpoint) *as* specified below *in Sections 6.4.1 and Section 6.4.2*. All models *(except for time to first severe or moderate COPD exacerbation)* will include as covariates: treatment group, biomarker subgroup (as defined in Section 6), treatment group by biomarker subgroup interaction, baseline history of COPD exacerbations within the last 12 months (1, >1 event), baseline COPD medications (double vs triple therapy), smoking status (current, former), bronchodilator reversibility (present, absent), and geographical region *(American Continent, ROW)* as covariates. The study is sized to obtain point estimates and confidence intervals for treatment group differences *within* the biomarker-high subgroup, but not to detect treatment efficacy differences *between* biomarker-high and biomarker-low subgroups (test of biomarker subgroup by treatment group interaction effect).

All continuous endpoints measured at multiple visits will be analyzed using a mixed-effect model repeated measurement (MMRM) model. All *such* models will in addition to the above covariates include visit, visit by treatment group interaction, visit by biomarker subgroup interaction, biomarker subgroup by treatment group interaction, treatment group by visit interaction, and three-way visit by biomarker subgroup by treatment group interaction as covariates. Therefore, missing data will be handled by the model under the missing-at-random assumption without need for imputation for early discontinuation.

The primary and secondary objectives in this study will be assessed in the biomarker-high population. *Models will include both biomarker-high and biomarker-low groups. Treatment effect estimates in both biomarker groups will be provided.*

Testing of the effect of lebrikizumab compared with placebo on a given endpoint within both biomarker-high and biomarker-low subgroups will be performed via *a Wald* at the two-sided $\alpha = 0.20$ level of the between-group least squares mean (LSM) differences with the LSMESTIMATE statement in SAS. Two tests for each endpoint (one treatment comparison per biomarker subgroup) will be performed and p-values reported with no adjustment for multiplicity. Point and interval estimates of LSMs within each treatment/biomarker subgroup combination will be presented.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint for this study is the absolute change in pre-bronchodilator FEV_1 (volume) from baseline to Week *12*. The baseline pre-bronchodilator FEV_1 measurement is defined as the last spirometry measurement prior to or on the day of randomization. The primary endpoint will be analyzed using a MMRM model as specified in Section 6.4 *and assessments after Week 12 will be excluded from the MMRM model.* Baseline pre-bronchodilator FEV_1 will be included as an additional covariate. *Missing data will be handled by the model under the missing-at-random assumption without need for imputation for early discontinuation.* The treatment effect will be tested within each biomarker subgroup according to the procedure specified in Section 6.4. *Point and interval estimates of the change from baseline of pre-bronchodilator FEV1 within each treatment group/biomarker group combination as well as of the difference in change from baseline of pre-bronchodilator FEV1 between treatment groups within each biomarker subgroup will be presented. A sensitivity analysis with respect to protocol adherence will be performed by excluding data collected more than 6 weeks after last study drug administration.*

The assessment optimal cutoff for the biomarker-high group will be explored.

6.4.2 Secondary Efficacy Endpoints

Rate of Moderate or Severe COPD Exacerbations

For each treatment/biomarker subgroup combination, the unadjusted annualized rate of COPD exacerbations will be estimated by the total number of exacerbations observed during the period defined as starting at the date of randomization and ending at most 172 days after randomization (including data collected during safety follow-up in the case of early drug discontinuation) regardless of adherence to study drug divided by the total patient-weeks at risk divided by 52 weeks per year.

Using exacerbations observed from randomization to at most 172 days post-randomization (including data collected during safety follow-up in the case of early drug discontinuation), the within-biomarker subgroup covariate-adjusted exacerbation rates (LSMs) of each treatment group will be estimated using a *Poisson* model *with overdispersion. Missing data will be handled by the model under the missing at random assumption, without imputation for early study discontinuation.* In addition to the covariates specified in Section 6.4, the model will also include a log-transformed years-at-risk as an offset variable, without imputation for early discontinuation. *If for any*

baseline covariate level there are no COPD exacerbations observed in the analysis population resulting in non-convergence of the model fitting algorithm, that covariate will be dropped from the analysis. The treatment effect will be tested within each biomarker subgroup according to the procedure specified in Section 6.4. *A sensitivity analysis with respect to early treatment discontinuation will be performed by excluding data collected more than 6 weeks after last study drug administration. Sensitivity of results to parametric model assumptions will be assessed by fitting a negative-binomial regression model.*

The assessment optimal cutoff for the biomarker-high group will be explored.

Absolute Change in Post-Bronchodilator FEV_1

The same procedure outlined for the primary endpoint in Section 6.4.1 will be followed to analyze the change from baseline to Week 24 in post-bronchodilator FEV_1.

Absolute Change in Pre-Bronchodilator FEV_1

The same procedure outlined for the primary endpoint in Section 6.4.1 will be followed to analyze the change from baseline to Week 24 in pre-bronchodilator FEV_1.

Time to First Moderate or Severe COPD Exacerbation

The covariate-adjusted hazard ratios of treatment groups within biomarker subgroups will be tested using a Cox proportional hazard model *stratified by* covariates specified in Section 6.4*: biomarker group, baseline history of COPD exacerbations within the last 12 months (1, >1 event), baseline COPD medications (double vs. triple therapy), smoking status (current, former), bronchodilator reversibility (present, absent), and geographical region (American Continent, ROW). Biomarker by treatment interaction effect will be included as covariates.* Patients who do not experience a protocol-defined exacerbation will be censored at the date of their Week 24 visit or date of early discontinuation, whichever occurs first. The treatment effect will be tested within each biomarker subgroup according to the procedure specified in Section 6.4.

St. George's Respiratory Questionnaire for COPD Patients

Change in health-related quality of life from baseline to Week 24 will be assessed by the overall score of the SGRQ-C and analyzed using a MMRM model as specified in Section 6.4. Baseline SGRQ-C score will be included as an additional covariate. The treatment effect will be tested within each biomarker subgroup according to the procedure specified in Section 6.4.

EXAcerbations of Chronic Pulmonary Disease Tool

Change in symptoms from baseline to Week 24 will be assessed in two ways: by the overall EXACT score and the cough and sputum domain of the EXACT using two MMRM models as specified in Section 6.4. Baseline overall EXACT and baseline cough and sputum domain score will be included as additional covariates respectively in each model. The mean of measurements taken during each of the 7 days prior to a visit will

be used at that visit. The treatment effect will be tested within each biomarker subgroup according to the procedure specified in Section 6.4.

Baseline Dyspnea Index and Transition Dyspnea Index

Change in dyspnea at Week 24 will be assessed by the BDI and TDI and analyzed using a MMRM model as specified in Section 6.4. Baseline BDI score will be included as an additional covariate. The treatment effect will be tested within each biomarker subgroup according to the procedure specified in Section 6.4.

6.5 SAFETY ANALYSES

Safety analyses will include all patients who were randomized and received at least one dose of study drug, with treatment group for these analyses defined as assigned at randomization. Patients who received treatments different from the one assigned at randomization and possible impacts on the interpretation of any safety analyses will be discussed in the final study report. Safety will be assessed by adverse events, clinical laboratory evaluations, vital signs, and ECGs.

All adverse events will be classified according to MedDRA system organ class (SOC), high level term (HLT) and preferred term (PT), and will be tabulated with a breakdown event severity. Similar AE tabulations will be performed on those events assessed by the investigator as related to study drug. A treatment emergent adverse event is defined as any new adverse event reported or any worsening of an existing condition on or after the first dose of study drug. Treatment emergent adverse events will be summarized by treatment group. Cardiovascular events (nonfatal myocardial infarction, unstable angina, heart failure, stroke, or hospitalization for myocardial ischemia and death due to CV event) will be summarized by treatment group. Clinical laboratory data (serum chemistry, hematology evaluations, and urinalysis values) and vital signs will be summarized by descriptive statistics (e.g., mean, standard deviation, minimum and maximum) for each treatment group. Anti-therapeutic antibodies, at baseline and during the study, will be summarized. Descriptive statistics (e.g., mean, standard deviation, minimum and maximum) of ECG findings will be generated for each treatment group.

6.6 PHARMACOKINETIC ANALYSES

Mean serum concentration versus time data will be tabulated. The elimination half-life ($t_{1/2}$) will also be estimated, tabulated, and summarized (e.g., mean, standard deviation, minimum and maximum). Additional PK analyses and exploratory exposure-response analyses may be conducted as appropriate.

6.7 EXPLORATORY ANALYSES

The following exploratory endpoints will be summarized using descriptive statistics by treatment group.

- *Absolute change in pre-bronchodilator FEV_1 (liters) from baseline to Week 4*
- *Change in the 6MWT distance from baseline to Week 24*

- *Change from baseline in blood eosinophils, serum periostin, IgE, CCL-13, CCL-17, and CCL-18 will be summarized by descriptive statistics*
- *Change in the body mass index, airflow obstruction, dyspnea, and exercise capacity (BODE) index from baseline to Week 24*
- *Change in COPD rescue medication use from baseline to Week 24*

Other PD biomarkers listed in Section 3.4.4 will also be explored.

6.8 *INTERIM ANALYSES*

The interim safety analyses will be performed periodically and reviewed by the IMC.

The Sponsor may choose to conduct up to two interim efficacy analyses. The decision to conduct an optional interim efficacy analysis and the timing of the interim efficacy analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim efficacy analysis. The interim efficacy analysis will be performed and interpreted by members of the Sponsor study team and appropriate senior management personnel who will be unblinded at the treatment group level. Access to treatment assignment information will follow the Sponsor's standard procedures.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and other electronic data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

ePRO data will be collected through use of an electronic device provided by an ePRO vendor. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR Part 11). The ePRO device data are available for view access only via secure access to a web server. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have

view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Data from paper PRO questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

Patients will use two ePRO devices, a handheld and a tablet, to capture PRO data for the SGRQ-C and EXACT instruments. A site interviewer will use the tablet to record the patient responses to the BDI and TDI. These data will be transmitted via the mobile network for the eDiary device to a centralized database at the eDiary vendor. These data can be reviewed by site staff via secure access to a web portal. Regular data transfers will occur from the centralized database at the vendor to the database at the Sponsor.

Once the study is complete, the eDiary data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all patient data in a machine-readable format on a compact disc.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate

and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ePRO data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union (E.U.) or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored by Roche. Approximately 70 sites will participate to enroll a total of approximately 300 patients.

An IxRS will be used to assign screening numbers, run-in numbers, randomize patients, monitor enrollment and patient status, and to manage study drug inventory, requests, and shipments.

Patient data will be recorded via an EDC system from Medidata Solutions (New York, NY) using eCRFs (see Section 7.2).

An eDiary vendor will provide handheld eDiaries and tablet devices to be used in this study (see Section 7.3).

Samples for urine pregnancy tests will be analyzed at the local laboratory. Samples for PD, PK, and antibody tests will be sent to the Sponsor or a designee for analysis. All other samples will be sent to one or several central laboratories for analysis.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site: http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf.

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Assessments

	Screening	24-Week Placebo-Controlled Period								Safety Follow-Up				
Week	–2	0	1	4	8	12	16	20	24	28	36			
Day (Assessment Window)	–14	1 (±3)	8 (±2)	29 (±3)	57 (±3)	85 (±3)	113 (±3)	141 (±3)	169 (±3)	197 (±7)	253 (±7)			
Visit	1	2	3	4	5	6	7	8	9	10	11	DT [a]	ET [b]	UV
Informed consent [c]	x													
Randomization		x												
SGRQ-C [d]		x				x			x		x	x	x	
EXACT [d]		x		x	x	x	x	x	x	x	x	x	x	
BDI [d]		x												
TDI [d]				x		x			x		x	x	x	
mMRC [d]	x	x				x			x		x	x	x	
Demographics	x													
Medical history [e]	x													
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Tobacco use	x	x	x	x	x	x	x	x	x	x	x	x	x	
Smoking cessation counseling [f]	x													
COPD exacerbations			x	x	x	x	x	x	x	x	x	x	x	x
Health care utilization			x	x	x	x	x	x	x	x	x	x	x	x

Appendix 1
Schedule of Assessments (cont.)

	Screening	24-Week Placebo-Controlled Period								Safety Follow-Up				
Week	–2	0	1	4	8	12	16	20	24	28	36			
Day (Assessment Window)	–14	1 (±3)	8 (±2)	29 (±3)	57 (±3)	85 (±3)	113 (±3)	141 (±3)	169 (±3)	197 (±7)	253 (±7)			
Visit	1	2	3	4	5	6	7	8	9	10	11	DT [a]	ET [b]	UV
Adverse events/ adverse events of special interest [g]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Weight	x								x			x	x	
Height	x													
Physical examination	x													
Limited physical examination [h]		x							x		x	x	x	
Single ECG [i]	x	x							x		x	x	x	
Vital signs [j]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
eDiary provided [k]	x													
Site review of eDiary data		x	x	x	x	x	x	x	x	x	x	x	x	
Chest X-ray [l]	x													
Spirometry [m]	x	x	x	x	x	x			x	x	x	x	x	
Post-bronchodilator spirometry	x	x				x			x		x	x	x	
6-minute walk test [n]		x				x			x			x	x	

Appendix 1
Schedule of Assessments (cont.)

	Screening	24-Week Placebo-Controlled Period								Safety Follow-Up				
Week	–2	0	1	4	8	12	16	20	24	28	36			
Day (Assessment Window)	–14	1 (±3)	8 (±2)	29 (±3)	57 (±3)	85 (±3)	113 (±3)	141 (±3)	169 (±3)	197 (±7)	253 (±7)			
Visit	1	2	3	4	5	6	7	8	9	10	11	DT [a]	ET [b]	UV
Serum pregnancy test [o]	x													
Urine pregnancy test [p]		x		x	x	x	x	x	x		x	x	x	
Hematology [q]	x	x	x	x	x	x			x	x	x	x	x	
Serum chemistry [r]	x	x				x			x		x	x	x	
Urinalysis [s]	x	x							x		x	x	x	
Urine cotinine [t]	x	x				x			x			x	x	
Serum PK sample [u]		x	x	x		x			x	x	x	x	x	
Serum periostin and PD sample [v]	x	x	x	x	x	x			x	x	x	x	x	
Serum antibody sample [u]		x		x		x			x		x	x	x	
Plasma PD sample [w]		x				x			x		x	x	x	
Optional whole blood RNA PAXgene sample [x]		x	x			x			x		x	x	x	

Appendix 1
Schedule of Assessments (cont.)

	Screening	24-Week Placebo-Controlled Period								Safety Follow-Up				
Week	–2	0	1	4	8	12	16	20	24	28	36			
Day (Assessment Window)	–14	1 (±3)	8 (±2)	29 (±3)	57 (±3)	85 (±3)	113 (±3)	141 (±3)	169 (±3)	197 (±7)	253 (±7)			
Visit	1	2	3	4	5	6	7	8	9	10	11	DT [a]	ET [b]	UV
Optional Whole blood DNA [x]		x												
Study drug administration		x		x	x	x	x	x						

6-MWT = six-minute walk test; COPD = chronic obstructive pulmonary disease; DT = dosing termination; ET = early termination; EXACT = EXAcerbations of Chronic Pulmonary Disease Tool; mMRC = mixed-effect model repeated measurement; PD = pharmacodynamics; PK = pharmacokinetic; PRO = patient-reported outcome; RCR = Roche Clinical Repository; SGRQ-C = Saint George's Respiratory Questionnaire-COPD; UV = unscheduled visit.

[a] The DT visit applies to patients who discontinue study drug prematurely and are unwilling to continue with study assessments in the placebo-controlled period. The DT visit should take place 4 weeks (± 3 days) after the last dose of study drug. Patients should then return for the first safety follow-up visit (Visit 10) 4 weeks after the DT visit.

[b] The ET visit applies to patients who are unwilling to return for safety follow-up visits and withdraw from the study. The early termination visit should take place 4 weeks (±7 days) after the last dose of study drug.

[c] Written informed consent for participation in the study must be obtained before performing any study-specific tests or evaluations.

[d] PRO questionnaires must be administered prior to the completion of other non-PRO assessments and before the patient receives any disease-status information or study drug during that visit. Patients will complete the EXACT at home for the 7 days prior to each study visit.

[e] Medical history will include clinically significant diseases and surgeries, smoking history, use of alcohol and drugs of abuse within the past year, and medication allergies. In particular, sites should record whether the patient has any history of anaphylaxis, cancer, cardiovascular disease, eosinophilic disease, inflammatory or autoimmune disease, and parasitic disease.

[f] For patients who are current smokers.

[g] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported.[h] Limited physical examination includes head, ears, eyes, nose, throat, cardiovascular, respiratory, and dermatological examinations.

[i] ECGs must be performed prior to any scheduled spirometry measurements, vital sign measurements, or blood draws.

[j] Includes temperature, heart rate, systolic and diastolic blood pressure, and respiratory rate. Blood pressure determinations should be made using the same arm with the patient in a seated or semi-supine position for all study visits.

[k] Patient is to be provided with an eDiary device. The eDiary will collect data on medication adherence, rescue medication use and the EXACT during the treatment period *(Week 24)*. Patients will complete the EXACT at home for the 7 days prior to each study visit.

[l] A chest X-ray must be performed or scheduled at Visit 1 unless a chest X-ray or CT scan has been *performed* within *6* months prior to Visit 1 and *the scan or radiologist report* is available for review by the investigator. The X-ray may be performed locally but *the scan or radiologist report* must be reviewed by the investigator prior to randomization at Visit 2. If a chest X-ray (or CT scan) is not available in the *6* months preceding Visit 1 or a chest X-ray cannot be completed during screening, the patient will not be eligible for the study.

[m] Pre-bronchodilator spirometry. Except for Visit 1, patients must withhold inhaled bronchodilator use within the specified window (see Section 4.5.1.12). For safety reasons, spirometry may be omitted if the patient is having an acute COPD exacerbation event at the time of the scheduled study visit.

[n] For safety reasons, the 6MWT may be omitted if the patient is unable or unwilling to perform the test.

[o] Serum pregnancy test is performed for all female patients of childbearing potential.

[p] Urine pregnancy test is performed at the site for all female patients of childbearing potential. If the urine pregnancy test result is positive, dosing should be withheld and a serum pregnancy test should be performed by the central laboratory. Once the pregnancy is confirmed, the patient must be discontinued from study drug (refer to Section 4.6.2).

[q] Includes hemoglobin, hematocrit, platelet count, WBC count, percentage and absolute differential counts (neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells).

[r] Includes sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase, creatine phosphokinase, and uric acid.

[s] Includes protein, blood, glucose, and microscopic (RBC, WBC, casts, and crystals).

[t] Patients who are current smokers and patients who are former smokers with tobacco cessation within 12 months of Visit 1.

[u] Whenever possible, an additional sample for serum PK and antibody analysis should be taken in the event of an anaphylactic, anaphylactoid, or serious hypersensitivity reaction.

[v] Periostin, IgE, CCL-13, CCL-17, CCL-18*, fibrinogen* and other IL-13– or COPD-related biomarkers will be measured. Novel IL-13– or

COPD-related biomarkers (if identified) may be measured from stored serum *and/or plasma*.

[w] The DNA and whole blood RNA PAXgene samples are optional and should only be obtained from patients who sign the separate RCR ICF.

Appendix 2
St. George's Respiratory Questionnaire for COPD Patients

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE
for COPD patients

(SGRQ-C)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life.
We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

ID: _____

Date: _____/_____/_____ (dd/mm/yy)

Before completing the rest of the questionnaire:

Please select one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

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continued…

St. George's Respiratory Questionnaire
PART 1

Questions about how much chest trouble you have.

Please select **ONE** box for each question:

Question 1. I cough:

most days a week	☐ a
several days a week	☐ b
only with chest infections	☐ c
not at all	☐ d

Question 2. I bring up phlegm (sputum):

most days a week	☐ a
several days a week	☐ b
only with chest infections	☐ c
not at all	☐ d

Question 3. I have shortness of breath:

most days a week	☐ a
several days a week	☐ b
not at all	☐ c

Question 4. I have attacks of wheezing:

most days a week	☐ a
several days a week	☐ b
a few days a month	☐ c
only with chest infections	☐ d
not at all	☐ e

Question 5. How many attacks of chest trouble did you have during the last year?

3 or more attacks	☐ a
1 or 2 attacks.....	☐ b
none	☐ c

Question 6. How often do you have good days (with little chest trouble)?

no good days.....	☐ a
a few good days	☐ b
most days are good	☐ c
every day is good.....	☐ d

Question 7. If you have a wheeze, is it worse in the morning?

no	☐
yes.....	☐

St. George's Respiratory Questionnaire
PART 2

8. ***How would you describe your chest condition?***

Please select ***ONE***:

Causes me a lot of problems or is the most important problem I have	☐ a
Causes me a few problems	☐ b
Causes no problem	☐ c

9. ***Questions about what activities usually make you feel breathless.***

For each statement please select ***the box*** that applies to you **these days**:

	True	False
Getting washed or dressed.....	☐	☐ a
Walking around the home.....	☐	☐ b
Walking outside on the level.....	☐	☐ c
Walking up a flight of stairs.....	☐	☐ d
Walking up hills.....	☐	☐ e

St. George's Respiratory Questionnaire
PART 2

10. ***Some more questions about your cough and breathlessness.***

For each statement please select ***the box*** that applies to you **these days**:

	True	False	
My cough hurts	☐	☐	a
My cough makes me tired	☐	☐	b
I am breathless when I talk	☐	☐	c
I am breathless when I bend over	☐	☐	d
My cough or breathing disturbs my sleep	☐	☐	e
I get exhausted easily	☐	☐	f

11. ***Questions about other effects that your chest trouble may have on you.***

For each statement please select ***the box*** that applies to you **these days**:

	True	False	
My cough or breathing is embarrassing in public	☐	☐	a
My chest trouble is a nuisance to my family, friends or neighbours	☐	☐	b
I get afraid or panic when I cannot get my breath	☐	☐	c
I feel that I am not in control of my chest problem	☐	☐	d
I have become frail or an invalid because of my chest	☐	☐	e
Exercise is not safe for me	☐	☐	f
Everything seems too much of an effort	☐	☐	g

St. George's Respiratory Questionnaire
PART 2

12. ***These are questions about how your activities might be affected by your breathing.***

For each statement please select ***the box*** that applies to you **because of your breathing**:

	True	False	
I take a long time to get washed or dressed.....	☐	☐	a
I cannot take a bath or shower, or I take a long time	☐	☐	b
I walk slower than other people, or I stop for rests.....	☐	☐	c
Jobs such as housework take a long time, or I have to stop for rests....	☐	☐	d
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐	e
If I hurry or walk fast, I have to stop or slow down	☐	☐	f
My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	☐	☐	g
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim.....	☐	☐	h

13. ***We would like to know how your chest trouble <u>usually</u> affects your daily life.***

For each statement please select ***the box*** that applies to you **because of your breathing**:

	True	False	
I cannot play sports or games	☐	☐	a
I cannot go out for entertainment or recreation	☐	☐	b
I cannot go out of the house to do the shopping	☐	☐	c
I cannot do housework	☐	☐	d
I cannot move far from my bed or chair.....	☐	☐	e

St. George's Respiratory Questionnaire

14. ***How does your chest trouble affect you?***

Please select ***ONE***:

It does not stop me doing anything I would like to do ..... ☐ a

It stops me doing one or two things I would like to do..... ☐ b

It stops me doing most of the things I would like to do..... ☐ c

It stops me doing everything I would like to do..... ☐ d

Thank you for filling in this questionnaire.

Before you finish, would you please check to see that you have answered all the questions.

Appendix 3
Exacerbations of Chronic Pulmonary Disease Tool

Description	Required Text	Translation
Title	EXACT Daily Diary	EXACT Daily Diary
DD	Daily Diary	Daily Diary
Q 1 of 14	Question 1 {1} of 14	Question 1 {1} of 14
Instructions	As you answer the following questions, please select the option that best describes your experience.	As you answer the following questions, please select the option that best describes your experience.
1		
	Did your chest feel congested today?	Did your chest feel congested today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
2		
	How often did you cough today?	How often did you cough today?
	Not at all	Not at all
	Rarely	Rarely
	Occasionally	Occasionally
	Frequently	Frequently
	Almost constantly	Almost constantly
3		
	How much mucus (phlegm) did you bring up when coughing today?	How much mucus (phlegm) did you bring up when coughing today?
	None at all	None at all
	A little	A little
	Some	Some
	A great deal	A great deal
	A very great deal	A very great deal

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Description	Required Text	Translation
4		
	How difficult was it to bring up mucus (phlegm) today?	How difficult was it to bring up mucus (phlegm) today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Quite a bit	Quite a bit
	Extremely	Extremely
5		
	Did you have chest discomfort today?	Did you have chest discomfort today?
	Not at all	Not at all
	Slight	Slight
	Moderate	Moderate
	Severe	Severe
	Extreme	Extreme
6		
	Did your chest feel tight today?	Did your chest feel tight today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
7		
	Were you breathless today?	Were you breathless today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely

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Description	Required Text	Translation
8		
	Describe how breathless you were today:	Describe how breathless you were today:
	Unaware of breathlessness	Unaware of breathlessness
	Breathless during strenuous activity	Breathless during strenuous activity
	Breathless during light activity	Breathless during light activity
	Breathless when washing or dressing	Breathless when washing or dressing
	Present when resting	Present when resting
9		
	Were you short of breath today when performing your usual personal care activities like washing or dressing?	Were you short of breath today when performing your usual personal care activities like washing or dressing?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
	Too breathless to do these	Too breathless to do these
10		
	Were you short of breath today when performing your usual indoor activities like cleaning or household work?	Were you short of breath today when performing your usual indoor activities like cleaning or household work?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
	Too breathless to do these	Too breathless to do these

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Description	Required Text	Translation
11		
	Were you short of breath today when performing your usual activities outside the home such as yard work or errands?	Were you short of breath today when performing your usual activities outside the home such as yard work or errands?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
	Too breathless to do these	Too breathless to do these
12		
	Were you tired or weak today?	Were you tired or weak today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
13		
	Last night, was your sleep disturbed?	Last night, was your sleep disturbed?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely

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Description	Required Text	Translation
14		
	How scared or worried were you about your lung problems today?	How scared or worried were you about your lung problems today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
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Training Material	Recommended Text	Translation (if available)
Standardized instruction given to patients with PDA training and with take-home instruction manual	Please complete your diary every evening, just before you go to bed.	Please complete your diary every evening, just before you go to bed.

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Appendix 4
Baseline/Transition Dyspnea Index

Baseline/Transition Dyspnea Index (BDI/TDI)

BASELINE DYSPNEA INDEX

Baseline Functional Impairment

_____Grade 4	*No Impairment*	Able to carry out usual activities and occupation without shortness of breath.
_____Grade 3	*Slight Impairment*	Distinct impairment in at least one activity but no activities completely abandoned. Reduction, in activity at work *or* in usual activities, that seems slight or not clearly caused by shortness of breath.
_____Grade 2	*Moderate Impairment*	Subject has changed jobs *and/or* has abandoned at least one usual activity due to shortness of breath.
_____Grade 1	*Severe Impairment*	Subject unable to work or has given up most or all usual activities due to shortness of breath.
_____Grade 0	*Very Severe Impairment*	Unable to work *and* has given up most or all usual activities due to shortness of breath.
_____W	*Amount Uncertain*	Subject is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categorised.
_____X	*Unknown*	Information unavailable regarding impairment.
_____Y	*Impaired for Reasons Other than Shortness of Breath*	For example, musculoskeletal problem or chest pain.

Usual activities refer to requirements of daily living, maintenance or upkeep of residence, yard work, gardening, shopping, etc.

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Baseline Magnitude of Task

_____Grade 4	*Extraordinary*	Becomes short of breath only with extraordinary activity such as carrying very heavy loads on the level, lighter loads uphill, or running. No shortness of breath with ordinary tasks.
_____Grade 3	*Major*	Becomes short of breath only with such major activities as walking up a steep hill, climbing more than three flights of stairs, or carrying a moderate load on the level.
_____Grade 2	*Moderate*	Becomes short of breath with moderate or average tasks such as walking up a gradual hill, climbing fewer than three flights of stairs, or carrying a light load on the level.
_____Grade 1	*Light*	Becomes short of breath with light activities such as walking on the level, washing, or standing.
_____Grade 0	*No Task*	Becomes short of breath at rest, while sitting, or lying down.
_____W	*Amount Uncertain*	Subject's ability to perform tasks is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categorised.
_____X	*Unknown*	Information unavailable regarding limitation of magnitude of task.
_____Y	*Impaired for Reasons Other than Shortness of Breath*	For example, musculoskeletal problem or chest pain.

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Baseline Magnitude of Effort

_____Grade 4	*Extraordinary*	Becomes short of breath only with the greatest imaginable effort. No shortness of breath with ordinary effort.
_____Grade 3	*Major*	Becomes short of breath with effort distinctly submaximal, but of major proportion. Tasks performed without pause unless the task requires extraordinary effort that may be performed with pauses.
_____Grade 2	*Moderate*	Becomes short of breath with moderate effort. Tasks performed with occasional pauses and requiring longer to complete than the average person.
_____Grade 1	*Light*	Becomes short of breath with little effort. Tasks performed with little effort or more difficult tasks performed with frequent pauses and requiring 50-100% longer to complete than the average person might require.
_____Grade 0	*No Effort*	Becomes short of breath at rest, while sitting, or lying down.
_____W	*Amount Uncertain*	Subject's exertional ability is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categorised.
_____X	*Unknown*	Information unavailable regarding limitation of effort.
_____Y	*Impaired for Reasons Other than Shortness of Breath.*	For example, musculoskeletal problems, or chest pain.

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TRANSITION DYSPNEA INDEX

Change in Functional Impairment

_____-3	*Major Deterioration*	Formerly working and has had to stop working and has completely abandoned some of usual activities due to shortness of breath.
_____-2	*Moderate Deterioration*	Formerly working and has had to stop working or has completely abandoned some of usual activities due to shortness of breath.
_____-1	*Minor Deterioration*	Has changed to a lighter job and/or has reduced activities in number or duration due to shortness of breath. Any deterioration less than preceding categories.
_____ 0	*No Change*	No change in functional status due to shortness of breath.
_____+1	*Minor Improvement*	Able to return to work at reduced pace or has resumed some customary activities with more vigour than previously due to improvement in shortness of breath.
_____+2	*Moderate Improvement*	Able to return to work at nearly usual pace and/or able to return to most activities with moderate restriction only.
_____+3	*Major Improvement*	Able to return to work at former pace and able to return to full activities with only mild restriction due to improvement of shortness of breath.
_____ Z	*Further Impairment for Reasons Other than Shortness of Breath*	Subject has stopped working, reduced work, or has given up or reduced other activities for other reasons. For example, other medical problems, being "laid off" from work, etc.

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Change in Magnitude of Task

_____-3	*Major Deterioration*	Has deteriorated two grades or greater from baseline status.
_____-2	*Moderate Deterioration*	Has deteriorated at least one grade but fewer than two grades from baseline status.
_____-1	*Minor Deterioration*	Has deteriorated less than one grade from baseline. Subject with distinct deterioration within grade, but has not changed grades.
_____ 0	*No Change*	No change from baseline.
_____+1	*Minor Improvement*	Has improved less than one grade from baseline. Subject with distinct improvement within grade, but has not changed grades.
_____+2	*Moderate Improvement*	Has improved at least one grade but fewer than two grades from baseline.
_____+3	*Major Improvement*	Has improved two grades or greater from baseline.
_____ Z	*Further Impairment for Reasons Other than Shortness of Breath*	Subject has reduced exertion capacity, **but** not related to shortness of breath. For example, musculoskeletal problem or chest pain.

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Change in Magnitude of Effort

_____-3	*Major Deterioration*	Severe decrease in effort from baseline to avoid shortness of breath. Activities now take 50-100% longer to complete than required at baseline.
_____-2	*Moderate Deterioration*	Some decrease in effort to avoid shortness of breath, although not as great as preceding category. There is greater pausing with some activities.
_____-1	*Minor Deterioration*	Does not require more pauses to avoid shortness of breath, but does things with distinctly less effort than previously to avoid breathlessness.
_____ 0	*No Change*	No change in effort to avoid shortness of breath.
_____+1	*Minor Improvement*	Able to do things with distinctly greater effort without shortness of breath. For example, may be able to carry out tasks somewhat more rapidly than previously.
_____+2	*Moderate Improvement*	Able to do things with fewer pauses and distinctly greater effort without shortness of breath. Improvement is greater than preceding category, but not of major proportion.
_____+3	*Major Improvement*	Able to do things with much greater effort than previously with few, if any, pauses. For example, activities may be performed 50-100% more rapidly than at baseline.
_____ Z	*Further Impairment for Reasons Other than Shortness of Breath*	Subject has reduced exertional capacity, but not related to shortness of breath. For example, musculoskeletal problem or chest pain.

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Appendix 5
Modified Medical Research Council Dyspnea Scale

Modified Medical Research Council Dyspnea Scale

Please select the statement that best describes you with respect to your COPD.

__“I only get breathless with strenuous exercise.”

__“I get short of breath when hurrying on the level or up a slight hill.”

__“I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level.”

__“I stop for breath after walking 100 yards or after a few minutes on the level.”

__“I am too breathless to leave the house.”

Appendix 6
Six-Minute Walk Test

The six-minute walk test (6MWT) will be conducted as per the study 6MWT Procedural Manual that is based on the 2002 ATS guidelines for the Six-Minute Walk Test (ATS Statement 2002).

Absolute contraindications to the 6MWT include unstable angina or myocardial infarction during the previous month.

Relative contraindications to participation in the 6MWT include:

- Resting heart rate > 120 per minute
- Systolic blood pressure > 180 mmHg
- Diastolic blood pressure > 100 mmHg

Supplemental oxygen flow rate will be recorded before every 6MWT. Heart rate, oxygen saturation (SpO_2), and the Borg Category Ratio 10 (CR10) Scale® will be recorded immediately before and after the procedure.

6MWT procedures will occur with the patient receiving the O_2 flow rate as determined by the screening oxygen titration protocol. Patients that are prescribed a different oxygen requirement either at rest or with exercise should be placed on the flow rate determined during the titration protocol. SpO_2 should be measured before all study-related 6MWTs after the patient has been at rest for 5 minutes while receiving their titrated O_2 requirement. Any patient who has an SpO_2 of < 85% after 5 minutes should not undergo the procedure during that visit.

SpO_2 should not be monitored during the 6MWT procedure. Patients should immediately stop the 6MWT procedure if any of the following occur:

- Chest pain
- Light headedness
- Intolerable dyspnea
- Leg cramps
- Staggering
- Diaphoresis
- Pale or ashen appearance
- Mental confusion or headache

Appendix 7
Borg Category Ratio 10 Scale®

Instruction. Use this rating scale to report how strong your perception is. It can be exertion, pain or something else. First look at the verbal expressions. Start with them and then the numbers. Of these ten (10) or ”Extremely strong”, “Maximal” is a very important intensity level. This is the most intense perception or feeling you have ever had.

If your experience or feeling is “Very weak”, you should say “1”, if it is “Moderate”, say “3”. Note that “Moderate” is “3” and thus weaker than “Medium”, “Mean” or “Middle”. If the experience is “Strong” or “Heavy” (it feels “Difficult”) say “5”. Note that “Strong” is about half of “Maximal”. If your feeling is “Very strong”, choose a number from 6 to 8. If your perception or feeling is stronger than ”10”, - “Extremely strong”, “Maximal” – you can use a larger number, e.g. 12 or still higher (that’s why “Absolute maximum” is marked with a dot “•”).

It's very important that you report what you actually experience or feel, not what you think you should report. Be as spontaneous and honest as possible and try to avoid under- or overestimating. Look at the verbal descriptors and then choose a number.

When rating exertion give a number that corresponds to how hard and strenuous you perceive the work to be. The perception of exertion is mainly felt as strain and fatigue in your muscles and as breathlessness or any aches.

0 ”Nothing at all”, means that you don’t feel any exertion whatsoever, no muscle fatigue, no breathlessness or difficulties breathing.

1 “Very weak” means a very light exertion. As taking a shorter walk at your own pace.

3 “Moderate” is somewhat but not especially hard. It feels good and not difficult to go on.

5 “Strong”. The work is hard and tiring, but continuing isn't terribly difficult. The effort and exertion is about half as intense as “Maximal”.

7 “Very strong” is quite strenuous. You can still go on, but you really have to push yourself and you are very tired.

10 “Extremely strong – Maximal” is an extremely strenuous level. For most people this is the most strenuous exertion they have ever experienced previously in their lives.

● Is ”Absolute maximum” for example ”12” or even more.

Any questions?

Borg CR10 scale®
© G. Borg, 1998, 2007
English

SAMPLE

0	Nothing at all	
0.3		
0.5	Extremely weak	Just noticeable
0.7		
1	Very weak	
1.5		
2	Weak	Light
2.5		
3	Moderate	
4		
5	Strong	Heavy
6		
7	Very strong	
8		
9		
10	Extremely strong	"Maximal"
11		
✦		
●	Absolute maximum	Highest possible

Borg CR10 Scale®
© Gunnar Borg, 1982, 1998, 2004
English

SAMPLE

Appendix 8
Childbearing Potential, Pregnancy Testing, and Contraception

All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening and a urine pregnancy test prior to administration of study drug at subsequent visits. If a urine pregnancy test is positive, study drug will not be administered that day. The result must be confirmed by a serum pregnancy test (conducted by the central laboratory). Refer to Section 5.4.3.1 of the protocol for management of a patient with a confirmed pregnancy.

All female patients are considered to be of childbearing potential *if they are postmenarcheal or have not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause) and have not undergone surgical sterilization (removal of ovaries and/or uterus).*

Female patients of reproductive or childbearing potential who are unwilling to use a highly effective method of contraception for the duration of the study will be excluded from study participation.

Examples of *non-hormonal* contraceptive methods with a failure rate of <1% per year include *bilateral* tubal ligation, male *sterilization, established proper use of hormonal contraceptives* that *inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices*.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Appendix 9
Clinical Criteria for Diagnosing Anaphylaxis

These criteria are taken from a summary report from the second symposium on the definition and management of anaphylaxis, conducted by the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network.

Anaphylaxis is highly likely when any one of the following three criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   AND AT LEAST ONE OF THE FOLLOWING:

   - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   - Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

   - Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
   - Reduced blood pressure or associated symptoms (e.g., hypotonia, syncope, incontinence)
   - Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):

   - Infants and children: low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure
   - Adults: systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that person's baseline