

PROTOCOL

TITLE: A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, STUDY TO ASSESS THE EFFICACY AND SAFETY OF LEBRIKIZUMAB IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS

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PROTOCOL AMENDMENT APPROVAL

Approver's Name

[REDACTED]

Title

Company Signatory

Date and Time (UTC)

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PROTOCOL AMENDMENT, VERSION 7: RATIONALE

Protocol GB28547, Version 7, was amended as follows:

- The Statistical Analysis Plan was amended on 16MAY2016 prior to unblinding to the study treatment in Cohort A to change the objectives, endpoints, and statistical methods to incorporate the [REDACTED] after the approval of Esbriet and Ofev for idiopathic pulmonary fibrosis. These changes were added to the protocol in this amendment (Section 2.1, Section 3.3.1.1, Section 3.3.1.2, Section 3.3.4, Section 6.1, Section 6.4.1, Section 6.4.2, and Section 6.5.1).
- The randomization for Cohort B is modified to be stratified by region, baseline lung function, and baseline serum periostin concentration. Stratification by prior pirfenidone exposure was introduced in Protocol Amendment 6 which was at 6 months after the start of enrollment into Cohort B. This factor is removed because this additional factor could not be implemented in the interactive voice/Web response system prior to completion of enrollment (Section 3.1.1).
- An Internal Monitoring Committee was added for an unplanned interim analysis of the efficacy and safety data of Cohort B (Section 3.1.3) and subsequent results were shared with the independent Data Monitoring Committee.
- The safety information for lebrikizumab was updated with the summary results from three completed Phase III asthma studies and two Phase II studies in atopic dermatitis (Section 1.2).
- The benefit-risk profile for lebrikizumab was updated on the basis of the totality of data from completed studies (Section 1.4).
- Optional biosensor assessment sections were removed because the manufacturer of the sensor has decommissioned this platform and it is no longer available.

Additional minor changes have been made to improve clarity and consistency and to align the protocol with the Sponsor's current internal guidelines and standard operating procedures. Substantive new information appears in italics.

PROTOCOL AMENDMENT, VERSION 7: SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

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

SECTION 1.1: BACKGROUND ON IDIOPATHIC PULMONARY FIBROSIS

...Other commonly prescribed therapies *for IPF* including corticosteroid monotherapy, N-acetylcysteine, and combined corticosteroid (e.g., azathioprine or cyclophosphamide) therapy remain contraindicated (Raghu et al. 2011).

SECTION 1.2: BACKGROUND ON LEBRIKIZUMAB

In Phase I clinical studies, no consistent laboratory abnormalities, clinically significant ECG changes, or consistent changes in vital signs were observed. ~~Safety and efficacy information from three Phase II asthma studies supported the continued development of this molecule for the treatment of asthma.~~ Phase II studies in asthma, a disease...

The clinical data obtained to date from the Phase I and Phase II clinical studies supported an acceptable benefit-risk for continuing with the evaluation of lebrikizumab for the treatment of asthma. [REDACTED]

[REDACTED] Overall, no clinically important safety signals were consistently identified in the completed Phase II asthma studies. Injection-site reactions were reported in a greater proportion of lebrikizumab-treated patients, but these were all non-serious and in most cases did not require treatment. The injection-site reactions observed to date in ongoing and completed clinical trials have been consistent with the rate and severity of those reported with other biological SC injectable therapies.

Unblinded study results recently became available from three Phase III studies of patients with asthma, two Phase II studies of patients with atopic dermatitis and the current study of patients with IPF, which includes a placebo-controlled period for Cohort A. A total of 1798 patients were administered at least one dose of lebrikizumab in all these studies combined (1536 patients with asthma, 184 patients with atopic dermatitis, and 78 patients with IPF). [REDACTED]

SECTION 1.4: BENEFIT-RISK ASSESSMENT

Given the evidence supporting a key role for IL-13 in disease pathogenesis, there is a compelling rationale to consider targeted anti-IL-13 therapy in patients with IPF. ~~As suggested by the experience with uncontrolled asthma, in which IL-13 is hypothesized to be a major contributing factor, modulation of IL-13 can translate to clinical benefits—specifically, improvements in lung function and a potential for reduction in exacerbations (as described above).~~

The Sponsor unblinded the treatment assignment in Cohort A of the study in May 2016, and conducted the planned analysis of this placebo-controlled cohort to assess the benefit of lebrikizumab monotherapy in accordance with this protocol. No clinically-meaningful treatment difference was observed between the lung function endpoints; however, the trends that were observed for the 6-minute walk test (6MWT) distance and A Tool to Assess Quality of Life in Idiopathic Pulmonary Fibrosis (ATAQ-IPF) were in favor of treatment with lebrikizumab. There was no evidence of safety concerns in Cohort A and the cohort safety profile was generally consistent with the safety profile observed in previous asthma studies with lebrikizumab.

The Sponsor performed an interim futility analysis for Cohort B in August. Taken together, the Sponsor decided to continue the study for the Cohort A extension and Cohort B per the protocol.

At this time, the benefit-risk ratio ~~that justifies~~ supports the continuation of this Phase II study of lebrikizumab in patients with IPF.

SECTION 2.1: EFFICACY OBJECTIVES

The primary efficacy objective for this study is to evaluate lebrikizumab compared with placebo as monotherapy or as combination therapy with pirfenidone background compared with placebo in patients with IPF, as measured by the ~~absolute change from baseline to Week 52~~ *annualized rate of decline in percentage of predicted FVC over 52 weeks.*

The secondary efficacy objectives are to evaluate lebrikizumab compared with placebo as monotherapy or as combination therapy with pirfenidone background therapy compared with placebo in patients with IPF as measured by:

- The efficacy on the basis of PFS, pulmonary function, diffusion capacity, non-elective hospitalization for any cause, ~~and~~ acute IPF exacerbation, *proportion of patients with at least 10% decline in percentage of predicted FVC or death, and all cause death*

SECTION 2.4: EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To evaluate the efficacy of lebrikizumab compared with placebo as monotherapy or as combination therapy with pirfenidone compared with placebo in patients with IPF on the basis of ~~time to death, time to non-elective hospitalization from respiratory cause, time to addition of supplemental oxygen therapy;~~ changes in DL₆₆, and quantitative lung fibrosis (QLF) score on HRCT, *ATAQ*, and the BORG Category Ratio 10 Scale® (BORG CR10), and ~~the proportion of patients with at least 10% decline in percentage of predicted FVC or death~~ *time to first occurrence of the St. George's Respiratory Questionnaire (SGRQ) individual domain worsening as defined by reaching minimal important difference (MID; Swigris et al. 2010).*

SECTION 3.1.1: Overview of Study Design

At the end of the screening period, and applicable qualifying pirfenidone titration run-in period for patients requiring pirfenidone titration, eligible patients will be randomized in a 1:1 ratio within each cohort to double-blind treatment with SC lebrikizumab 250 mg or placebo. Dynamic hierarchical randomization will be performed centrally and stratified by region (United States, Europe/Canada, and other) ~~[limited to Cohort A]~~ or by prior pirfenidone exposure (~~none, < 1 year, > 1 year~~) ~~[limited to Cohort B]~~, lung function (FVC < 50%, 50% to 75%, > 75% predicted), and serum periostin concentration (< 50 ng/mL, ≥ 50 ng/mL) in each cohort.

SECTION 3.1.3: Internal Monitoring Committee

[REDACTED]

[REDACTED]

Details with regard to the IMC were documented in an IMC agreement.

SECTION 3.2.3: Rationale for Patient Population

...During the open-label lebrikizumab period, at the investigator's discretion, a patient can start background therapy, including use of pirfenidone or other treatment, provided that it is an ~~approved~~ therapy for IPF *approved* in the applicable region (e.g., European Union, Canada, Mexico, Peru, or Japan) (see Section 4.4.1.2)...

The Principal Investigator should notify the Medical Monitor of proposed changes in concomitant IPF therapy prior to starting rescue therapy *throughout the study for patients in either Cohort A or Cohort B.*

SECTION 3.2.5: Rationale for Control Group

During the placebo-controlled periods, N-acetylcysteine or IPF therapy approved by local regulatory authorities can be initiated only after a confirmed progression event ($\geq 10\%$ decrease in FVC or non-elective hospitalization). No other therapies for IPF can be started at any time during the study.

For patients assigned to Cohort B, other approved therapies may be initiated in the absence of disease progression if pirfenidone is stopped because of safety considerations (see Section 4.4.1.2).

SECTION 3.3.1.1: Primary Efficacy Outcomes Measure

The primary efficacy outcome measure for this study is the ~~absolute change from baseline to Week 52 in percent predicted FVC~~ *annualized rate of decrease in percentage of predicted FVC over 52 weeks (% FVC/year).*

SECTION 3.3.1.2: Secondary Efficacy Outcomes Measures

The secondary efficacy outcome measures for this study are as follows:

- ~~Change from baseline to Week 52~~ *Annualized rate of decline in 6MWT distance over 52 weeks*
- Time from randomization to first ~~decrease from baseline~~ *occurrence of a $\geq 10\%$ absolute decline in percentage of predicted FVC (~~L~~) or death from any cause*
- ~~Time from randomization to first~~ *Annualized rate of decrease from baseline of $\geq 15\%$ in percentage of predicted DL_{CO} (~~mL CO/min 1/mmHg 1~~) over 52 weeks*
- PFS, defined as the time from study treatment randomization to the first occurrence of any of the following *disease progression or death* events:
 - Death from any cause
 - ~~Non-elective~~ *All-cause hospitalization for any cause*
 - A decrease from baseline (*relative change*) of $\geq 10\%$ in FVC (*mL/year*) (~~relative change~~)
- Annualized rate of ~~change~~ *decrease in FVC (~~L~~) over a 52-week period (mL/year)*
- ~~Change from baseline to Week 52~~ *Annualized rate of decrease in ATAQ-IPF questionnaire total score over a 52-week period (see Appendix 5 for a description of the instrument)*
- ~~Change from baseline to Week 52 in~~ *Time from randomization to first occurrence of the SGRQ (see Appendix 5 for a description of the questionnaire) worsening (total score) as defined by reaching MID (Swigris et al. 2010): Total Score =7 or death from any cause*
- Time from randomization to non-elective hospitalization or death from any cause

- Time from randomization to first event of acute IPF exacerbation *as defined below:*

IPF exacerbation is defined as an event that meets all of the following criteria as determined by the investigator:

Unexplained worsening or development of dyspnea within the previous 30 days

***And** radiologic evidence of new bilateral ground-glass abnormality or consolidation superimposed on a reticular or honeycomb background pattern that is consistent with UIP*

***And** absence of alternative causes, such as left heart failure, pulmonary embolism, pulmonary infection (on the basis of endotracheal aspirate or bronchoalveolar lavage, if available, or investigator judgment), or other events leading to acute lung injury (e.g., sepsis, aspiration, trauma, reperfusion pulmonary edema)*

SECTION 3.3.4: Exploratory Outcome Measures

The exploratory outcome measures for this study include the following:

- ~~Change from baseline to Week 52 in DL_{CO} % predicted~~
- ~~Time from randomization to non-elective hospitalization for respiratory cause as determined by the investigator~~
- ~~Time from randomization to death~~
- ~~Time from randomization to addition of supplemental oxygen therapy for patients not receiving supplemental oxygen at baseline~~
- Change from screening (corresponding to timing for randomization strata) in serum and plasma biomarkers (e.g., periostin and CCL18) and change from baseline in serum and plasma biomarkers (e.g., periostin, CCL18, YKL40, COMP, OPN, CCL13)
- Exposure-response relationships (to be evaluated as warranted)
- ~~Change from baseline to Week 52 in physical activity as determined by biosensor technology~~
- Change from baseline to Week 52 in the ATAQ-IPF
- Time from randomization to first occurrence of SGRQ individual domain worsening as defined by reaching MID (Swigris et al. 2010): Symptom =8, Activity =5, Impact =7, or death from any cause
- ~~The proportion of patients with at least 10% decline in % predicted FVC or death by Week 52~~
- Change from baseline to Week 52 in the SGRQ

The analysis plan for the exploratory HRCT and biomarkers will be specified in a separate document.

SECTION 4.1: PATIENTS

Approximately 480 patients ≥ 40 years of age who have a diagnosis of IPF will be enrolled in this study.

SECTION 4.1.2: Exclusion Criteria

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

- Chronic oral corticosteroid therapy is not permitted within 4 weeks prior to screening (Visit 1) ~~or~~, during screening and run-in, *or throughout the study period*

SECTION 4.2: METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Dynamic hierarchical randomization will be performed centrally and stratified by region (United States, Europe/Canada, other), ~~[limited to Cohort A] or by prior pirfenidone exposure (none, < 1 year, > 1 year) [limited to Cohort B]~~, lung function (FVC $< 50\%$, 50% to 75% , $> 75\%$ predicted),...

As described in Section 6, treatment assignment will be unblinded to the personnel performing the analysis when all data for the primary endpoint period are in the database and the data have been cleaned and verified.

~~_____~~
However, patients and all study site personnel will remain blinded...

SECTION 4.4.1.1: Corticosteroids

Chronic maintenance oral corticosteroid therapy, defined as daily or alternate day oral corticosteroid maintenance therapy is not permitted within the 4 weeks prior to screening Visit 1, during screening *and run-in*, or throughout the study period....

SECTION 4.4.1.2: Rescue Therapy

Patients in Cohort A who experience confirmed disease progression ($\geq 10\%$ decline in FVC [*mL/year; relative change*] or non-elective hospitalization) during the placebo-controlled study period will be allowed, at the investigator's discretion, to start rescue therapy, including use of pirfenidone or other IPF treatment provided that it is an ~~approved~~ therapy for IPF *approved* in the applicable region (e.g., European Union, Canada, Mexico, Peru, or Japan). Patients who start rescue therapy will be allowed and encouraged to remain in the study and continue study treatment.

During the open-label lebrikizumab study period, at the investigator's discretion, a patient can initiate additional therapy for IPF that is approved in the applicable region (e.g., European Union, Canada, Mexico, Peru, or Japan) without evidence of disease progression.

Patients in Cohort B who experience a confirmed disease progression ($\geq 10\%$ decline in FVC [*mL/Year; relative change*] or non-elective hospitalization) during the placebo controlled study period should continue the study drug medication, including background

pirfenidone. However, at the investigator's discretion, the initiation of rescue therapy that is approved by local regulatory authorities is allowed. Combination treatment with pirfenidone and nintedanib is not permitted throughout the study, given lack of adequate safety information on this drug combination. *Patients in Cohort B may initiate other approved therapies in the absence of disease progression if pirfenidone is stopped because of safety considerations.* The Principal Investigator should notify the Medical Monitor of proposed changes in concomitant IPF therapy prior to starting rescue therapy for patients in either Cohort A or Cohort B throughout the study.

~~No other therapies for IPF may be started at any time during the study prior to experiencing a confirmed progression event.~~ Patients who start rescue therapy must begin appropriate monitoring per the prescribing information for that therapy. All safety laboratory assessments, including those required for the prescribed rescue medication, should be analyzed by the central laboratory utilized for the GB28547 clinical study.

SECTION 4.4.2: Prohibited Therapy

- Chronic oral corticosteroid therapy is not permitted within 4 weeks prior to screening (Visit 1), ~~or~~ during screening and *run-in*, or throughout the study period.
- N-acetylcysteine or IPF therapy approved by local regulatory authorities can be initiated in the event of disease progression as per Section 4.4.1.2. *Patients in Cohort B may initiate other approved IPF therapies in the absence of disease progression if pirfenidone is stopped because of safety considerations.*

SECTION 4.4.2.1: Prohibited Therapy Limited to Cohort B (Background Pirfenidone)

- Ongoing use of the following therapies or agents within 4 weeks of randomization (Day 1, Visit 2) or ~~during the study~~ *at the initiation of pirfenidone (whichever is longer) to the end of the safety follow-up period*

Strong inhibitors of CYP1A2 (e.g., fluvoxamine or enoxacin)

Moderate inducers of CYP1A2 limited to tobacco smoking and tobacco-related products

SECTION 4.5.12: Protocol-Defined Idiopathic Pulmonary Fibrosis Exacerbation

At each study visit, the investigator will ask directed questions and review the file to assess the possibility that the patient experienced an acute IPF exacerbation per protocol over the preceding 4 weeks. A dedicated eCRF will be used to record information regarding a protocol defined acute IPF exacerbation. An acute IPF exacerbation should also be reported as an adverse event (or serious adverse event as applicable) as per Section 5.2 and Section 5.3.5.9. ~~An~~ *protocol-defined* acute IPF exacerbation is defined as an event that meets **all** of the following criteria as determined by the investigator:

SECTION 4.5.14: Laboratory Assessments

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

- Serum samples for antibodies and anti-PLB2 *antibody* testing

~~SECTION 4.5.16: Optional Biosensor Assessment~~

~~Biosensors provide data on patients' physiologic status. Although a patient can accurately report on his or her well being and can rate some physiologic symptoms, patients may not be able to quantify other physiologic data. Biosensors have the potential to provide more accurate physiologic measurements.~~

BodyMedia Wireless Armband Biosensor

~~The bodymedia armband biosensor measures patient activity over time. The data collected will be compared with data from the 6MWT, ATAQ IPF and SGRQ to understand the correlation between the different data streams. Patient data will be downloaded at the sites during the patients' monthly visits. The biosensor assessment is limited to patients who provided consent for this substudy prior to publication of GB28547 protocol Version 5.~~

SECTION 5.1.1: Adverse Events of Special Interest for Lebrikizumab

Based on data to date, the theoretical risks associated with IL-13 inhibition, and the risks associated with and for biologic agents in general, *the following* four categories of potential adverse events have been identified as adverse events of special interest for lebrikizumab (refer to the Lebrikizumab IB for more details):~~The four categories are the following:...~~

The documentation and expedited reporting requirements for these adverse events of special interest are described in Section 5.2.2 (reporting of serious events) and Section 5.2.3 (reporting of ~~non-serious~~ events of special interest).

SECTION 5.1.1.1: Local Injection-Site Reactions

In *recently*-completed Phase ~~III~~ clinical trials with lebrikizumab administered to patients with asthma, *the reported rate of injection-site reactions were reported in a greater proportion of lebrikizumab treated patients than in placebo treated patients* *was comparable between the group of patients who were treated with lebrikizumab and the group of patients who were treated with placebo (117 of 1432 patients [8.2%] vs. 55 of 716 patients [7.7%], respectively). In Cohort A of Study GB28547 (RIFF), injection site reactions were reported in 13 of 78 patients (16.7%) who were treated with lebrikizumab compared with 6 of 76 patients (7.9%) who were treated with placebo.* These events were all non-serious and in most cases did not require treatment.

SECTION 5.1.1.2: Anaphylactic, Anaphylactoid, and Hypersensitivity Reactions

~~In completed Phase I/II clinical trials of lebrikizumab, no anaphylactic, anaphylactoid, or serious and hypersensitivity reactions were observed; however, anaphylaxis and~~

~~hypersensitivity reactions~~ to treatment are considered a potential risk with all biologic medications, including lebrikizumab. On the basis of newly-available safety data from six studies that were recently unblinded to the study treatment, there were no reports of anaphylaxis per the Sampson's criteria assessed as related to lebrikizumab treatment by an independent external adjudication committee that was blinded to the study treatment. Furthermore, in the study of patients with IPF (Study GB28547, Cohort A) and both atopic dermatitis studies (Study GS29250 and Study GS29735), there were no reported events of anaphylaxis, anaphylactoid, or serious hypersensitivity reactions meeting search criteria.

Patient injections will be administered by a qualified health care professional, ~~and/or a~~ trained non-health care professional who can legally administer injections. Patients will be monitored by a qualified health care professional for a minimum of 1 hour after dosing for the first three treatment visits and for 30 minutes after dosing for all ~~other~~ subsequent treatment visits.

SECTION 5.1.1.3: Infections

The role of IL-13 in other infections is less clear. ~~In the completed Phase III asthma studies of lebrikizumab, infections have not been associated with lebrikizumab. A single case of tuberculosis occurred in a patient living in an endemic area.~~ Safety analysis data from five studies (with the exclusion of Study GB28547) that were recently unblinded to the study treatment show that lebrikizumab treatment is not associated with infections and overall, there were no imbalances in infections (both broad and narrow [MedDRA High-Level Group Term of helminthic disorders, mycobacterial infectious disorders, and protozoal infectious disorders, or MedDRA High-Level Term of listeria infections]). Analysis results from Cohort A of Study GB28547 showed higher rates of infection (broad) in the group of patients who were treated with lebrikizumab versus those who were treated with placebo (51 of 78 patients [65.4%] vs. 41 of 76 patients [53.9%], respectively), which was driven mainly by an imbalance in urinary tract infections (UTIs) between the groups of patients. All patients who were treated with lebrikizumab and showed a UTI had predisposing risk factors, including a single serious adverse event of UTI that occurred in a patient with prostatic hyperplasia.

In Phase III studies of patients with moderate-to-severe asthma, herpes infections including herpes zoster (shingles) were reported in 2.0% of patients who were treated with lebrikizumab compared with 0.7% of patients who were treated with placebo. In a Phase II study of patients with moderate-to-severe atopic dermatitis, herpes infections including herpes zoster (shingles) were reported in 3.8% of the patients who were treated with lebrikizumab. None of the herpes infections that were reported, including herpes zoster, required a hospital admission. In Cohort A of Study GB28547, herpes viral infections in patients were reported but there were no imbalances noted between patients who were treated with lebrikizumab and patients who were treated with placebo. Refer to the Lebrikizumab IB for more detail.





SECTION 5.2: SAFETY PARAMETERS AND DEFINITIONS

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

SECTION 5.2.3: Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

~~Non-serious a~~ Adverse events of special interest 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). Adverse events of special interest for this study include the following:

- *Adverse events of special interest for pirfenidone*
 - Elevated liver enzymes (to report cases of elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Section 5.3.5.6)*
 - Photosensitivity reaction or rash*
 - Gastrointestinal disorders*

SECTION 5.3.1: Adverse Event Reporting Period

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until study completion. After this period, the investigator does not need to actively monitor patients for adverse events. Once the study has ended the Sponsor should be notified if the investigator becomes aware of any serious adverse events and ~~non-serious~~ adverse events of special interest (see Section 5.6).

For Cohort B only: Safety findings should be reported for patients who are administered background pirfenidone by their health care provider. Safety findings should be collected as of date of consent for the study for patients who are naive to

pirfenidone treatment. Safety findings should be collected on the dates when pirfenidone is taken (see Section 4.5.10).

SECTION 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:

- ~~Non-serious~~ Adverse events of special interest (see Section 5.4.2 for further details)

SECTION 5.4.2: Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

SECTION 5.4.2.1: Events Occurring prior to Initiation of Study Drug

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. A paper Serious Adverse Event/~~Non-Serious~~ Adverse Event of Special Interest CRF and Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), with use of the fax numbers provided to investigators. Patients who undergo screening procedures but do not enroll in the study will have serious adverse events recorded only in the Roche Drug Safety database and not in the study's clinical database.

SECTION 5.4.2.2: Events Occurring after Initiation of Study Drug

After initiation of study drug, serious adverse events and ~~non-serious~~ adverse events of special interest will be reported until study completion. 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.

For Cohort B only: Safety findings should be reported for patients who are administered background pirfenidone by their health care provider. Safety findings should be collected as of date of consent for the study for patients who are naive to pirfenidone treatment. Safety findings should be collected on the dates when pirfenidone is taken (see Section 4.5.10).

In the event that the EDC system is unavailable, a paper clinical trial Serious Adverse Event/~~Non-Serious~~ Adverse Event of Special Interest reporting form and Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee

immediately (i.e., no more than 24 hours after learning of the event), with use of the fax numbers or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

SECTION 5.5.2: Sponsor Follow-Up

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

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

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

SECTION 6: STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The analysis of data from the placebo-controlled period *for each cohort* will be performed when all patients have either completed the *end of the placebo-controlled treatment (Week 52/EOT)* visit or discontinued early from the study. Treatment assignment will be unblinded to the personnel performing the analysis when all data through the EOT visit are in the database and the data have been cleaned and verified *for each cohort*.

The analysis of complete data for the study, including data from the placebo-controlled period, open-label extension period for Cohort A, and the 14-week safety follow-up period, will be performed when all patients have either completed the placebo-controlled period, open-label extension period for Cohort A, and 14-week safety follow-up period or discontinued early from the study, all data from the study are in the database, and the database is locked. *An interim futility analysis of Cohort B was conducted (see Section 6.8).*

SECTION 6.1: DETERMINATION OF SAMPLE SIZE

In Cohort A, a sample size of 75 patients in each treatment group will provide ~~more than~~ *approximately 80%* power to detect a *change in the annualized rate of decline in percentage of predicted FVC over 52 weeks of a 7.93.7%* difference in the means of the absolute change from baseline in percentage of predicted FVC at 52 weeks, assuming that the common standard deviation is 8% (as reported in the placebo group in the ASCEND trial of pirfenidone) using a two group t-test with a 0.05 two-sided significance level.

In Cohort B, a sample size of 165 patients in each treatment group will provide ~~more than~~ *approximately 80%* power to detect a 2.5% difference in the ~~means of the absolute~~

~~change from baseline~~ annualized rate of decline in percentage of predicted FVC over 52 weeks, assuming that the common standard deviation is 8% (as reported in the ASCEND trial of pirfenidone) using a two group t-test with a 0.05 two-sided significance level.

SECTION 6.4: EFFICACY ANALYSES

However, the Sponsor study team directly involved in the study conduct (medical monitoring, clinical operations, drug safety, etc.) will not have access to individual treatment assignments until study completion (*see Section 3.1.3*), when all patients have completed the safety follow-up or discontinued the study. All non-Sponsor personnel who are involved in the conduct of the study (e.g., patients, site monitors, and investigators) will remain blinded to patient-specific treatment assignments until all patients complete the safety follow-up period or discontinue from the study.

SECTION 6.4.1: Primary Efficacy Endpoint

~~The primary efficacy endpoint for this study is the change from baseline to Week 52 in % predicted FVC~~ annualized rate of decrease in percentage of predicted FVC (% FVC/year) through Week 52.

The annualized rate of decrease in percentage of predicted FVC will be compared across the treatment arms with the use of a random slope model on observed cases at a 0.05 two-sided significance level.

~~The statistical analysis will be based on a linear mixed effects model with absolute change as the dependent variable. Independent variables will be baseline % predicted FVC, treatment arm, post baseline visit, treatment arm by visit interaction, and the stratification variables with the same categories used for the stratified randomization.~~

The statistical model is as follows:

$$FVC_{ijk} = (\beta_0 + \beta_{0k}) + (a_i * \beta_1 + \beta_{1k}) * t_k + \eta_k + \varepsilon_{ijk}$$

where FVC_{ijk} is the predicted FVC for k th patient at visit j in treatment group i ; β_0 is the intercept; a_i and β_1 is the interaction term of the treatment effect ($i = \text{lebrikizumab or placebo}$) and the slope; t_k is the assessment time (continuous in year) for patient k ; η_k is the effect of baseline lung function (defined as FVC <50% vs. 50% to 75% vs. >75% predicted) for the k th patient; β_{0k} and β_{1k} are the random components for intercept and slope; ε_{ijk} is the random error for k th patient at time j ; β_{0k} , β_{1k} and ε_{ijk} are assumed to be independent and normally distributed with mean 0 and variance of σ_0^2 , σ_1^2 and σ_ε^2 respectively.

Note that because of a relatively large number of strata defined by the randomization stratification factors, the analysis will be adjusted only for baseline lung function because baseline FVC may impact the clinical disease course.

~~From the model, least squares means for the absolute change from baseline as well as placebo corrected absolute changes with 95% confidence intervals for each treatment arm at each post baseline visit, annualized rate of decline in each treatment arm and the difference between the two treatment arms will be estimated, provided with 95% CIs. Missing data will be handled by the model under the missing at random assumption without need for imputation for early discontinuation. The model implicitly imputes missing data on the basis of a patient's estimated rate of worsening of lung function prior to the study visit discontinuation (i.e., under the assumption that it is missing at random).~~

SECTION 6.4.2: Secondary Efficacy Endpoints

The secondary efficacy end points of this study are as follows:

- PFS, defined as the time from study treatment randomization to the first occurrence of any of the following *disease progression or death* events:
 - Death from any cause
 - ~~Non-elective~~ All-cause hospitalization for any cause
 - A decrease from baseline (*relative change*) of $\geq 10\%$ in FVC (L)
- Annualized rate of ~~change~~ decrease in FVC (mL/year) over 52 weeks
- Time from randomization to first ~~decrease from baseline~~ occurrence of a $\geq 10\%$ in absolute decrease in percentage in predicted FVC (L) or death from any cause
- ~~Time from randomization to first~~ Annualized rate of decrease from baseline of $\geq 15\%$ in percentage of predicted DL_{CO} (mL CO/min 1/mmHg 1) ~~at Week 52~~ over 52 weeks
- ~~Change from baseline to Week 52~~ Annualized rate of decrease in the ATAQ-IPF total score over 52 weeks (see Appendix 5 for a description of the instrument)
- Time from randomization to non-elective hospitalization or death from any cause
- ~~Change from baseline to Week 52~~ Annualized rate of decrease in the 6MWT distance over 52 weeks
- Time from randomization to first event of acute IPF exacerbation (*defined below*)

IPF exacerbation is defined as an event that meets all of the following criteria as determined by the investigator:

Unexplained worsening or development of dyspnea within the previous 30 days

And radiologic evidence of new bilateral ground-glass abnormality or consolidation, superimposed on a reticular or honeycomb background pattern, that is consistent with UIP

And absence of alternative causes, such as left heart failure, pulmonary embolism, pulmonary infection (on the basis of endotracheal aspirate or bronchoalveolar lavage if available or investigator judgment), or other events that lead to acute lung injury (e.g., sepsis, aspiration, trauma, reperfusion pulmonary edema)

- ~~Change from baseline to Week 52 in the~~ Time from randomization to first occurrence of SGRQ (see Appendix 5 for a description of the questionnaire) worsening (total score) as defined by reaching MID (Swigris et al. 2010): Total Score = 7 or death from any cause
- Time from randomization to death from any cause

All continuous endpoints will be analyzed with the use of the same methodology as the primary endpoint (see previous section) *with specifics for models and summaries specified in the SAP.*

~~For time to event endpoints, a Cox Proportional Hazards (CPH) model will be performed to compare the treatment groups, with stratification variables included in the model as covariates. The log rank test stratified by baseline lung function (FVC <50% vs. 50% to 75% vs. >75% predicted) will be used to compare the time to event endpoints between the two treatment arms. Time will be measured relative to the date of study treatment randomization (Day 1). Patients who do not experience an the event during the treatment period will have their data censored at the time when they were last known to be event free (EOT visit) or at the time of early treatment discontinuation, whichever occurs earlier on the last date during the placebo-controlled period when, on the basis of the assessments in accordance with this protocol, the patient can be considered to have been event-free. Any patients who undergo lung transplantation will be censored at the date of the transplant. Sensitivity analyses will be provided with lung transplant counted as an event for PFS and time from randomization to death or non-elective hospitalization from any cause.~~

The primary efficacy assessments for the randomized placebo-controlled period are made on the study day of initiation of the open-label lebrikizumab through Week 52. Assessment on this day will be included for analyses of the randomized placebo-controlled period, but subsequent assessment during the open-label period or after Week 52 will be excluded.

~~The hazard ratio and its 95% CI will be estimated with the use of a Cox regression model stratified by baseline lung function. In fitting the CPH model, Efron's approach to the treatment of tied event times will be used (Therneau and Grambsch 2000). Under this model, the exponent of the regression coefficient that corresponds to the treatment group covariate represents the estimated hazard ratio (lebrikizumab vs. placebo). Inference will focus on estimating this hazard ratio and a corresponding 95% CI based on the PH regression model. Risk rates at Week 52 by treatment group will be estimated with the use of In fitting the Cox model, ties will be handled with the approximate likelihood method of Efron (1977). Kaplan-Meier curves for PFS, and p-values comparing the two curves based on the score test statistic will be reported~~ *will be provided.*

Summary statistics of the ~~PRO~~ATAQ-IPR and SGRQ endpoints and the changes from baseline will be calculated at each assessment time-point for each treatment group. The mean, standard error, and median of the absolute scores and the mean changes from baseline (and 95% CIs) between treatment groups will be reported for the endpoint. For scores involving change from baseline, patients without baseline values will be excluded from the analyses. Line charts depicting the means and mean changes of subscales over time will be also provided. Scoring for the questionnaire will be based on relevant user manuals.

Frequencies and percentages of missing data for the ~~PRO~~ATAQ-IPR and SGRQ endpoints will be compared between the two treatment arms. ~~Differences in the proportion of dropouts (defined as patients withdrawing from treatment for reasons other than documented disease progression or death) between the two treatment arms will be tested using the χ^2 test.~~

~~The PRO endpoints assessed at multiple timepoints will be analyzed using mixed model repeated measures. Each model will have an intercept term, a linear time trend term (in weeks), a term for treatment group, and a term for treatment by time interaction. A baseline score and appropriate covariates will also be added.~~

~~For all endpoints, treatment effects will be summarized using point estimates and corresponding two-sided 95% CIs will be provided.~~

Additional details for summarization, sensitivity analyses, and type I error control are provided in the SAP.

SECTION 6.5: SAFETY ANALYSES

Safety analyses will be based on all patients who received at least one dose of *randomized* study drug, with patients grouped according to the actual treatment received. Safety summaries will be presented by treatment arm for all treated patients. *In addition, safety listings will be provided for any events reported during pirfenidone exposure prior to randomization.*

Safety will be assessed through the summary of adverse events, laboratory test results, (including antibodies to lebrikizumab), ECG, and vital signs. These summaries will be produced separately for *each cohort* for the treatment period (placebo-controlled study treatment period, the *Cohort A* open-label lebrikizumab period) ~~and the 14 week safety follow-up period.~~

SECTION 6.5.1: Adverse Events

~~Specific analyses~~ will be performed ~~for~~ *by treatment group for events of special interest that include anaphylactic reactions, local injection-site reactions, infections, and malignancies:*

- ~~a~~ Anaphylactic reactions using both the MedDRA "anaphylactic reaction" Standardized MedDRA Query and Sampson's Criteria (see Appendix 7) *will be reviewed and adjudicated by independent, external experts accordingly to a charter.*
- Local injection-site reactions, ~~defined through coding (any verbatim term that includes "injection site") and~~ *will be identified with the use of the MedDRA high-level term of "injection site reaction", will also be analyzed by treatment arm and severity, as well as by whether study drug was discontinued as a result of the reaction.*
- ~~The rate of~~ Infections, as identified *with the use of the MedDRA system organ class of "infections and infestations", will be summarized for each treatment arm.*
- ~~Events that occur in the MedDRA neoplasms, benign, malignant, and unspecified (including cysts and polyps) system organ class will also be summarized for each treatment arm.~~ *Malignancies, as identified on the basis of the MedDRA SMQ of "Malignancy" and the subSMQ of "Malignant and unspecified tumours"*

SECTION 6.6: PHARMACOKINETIC ANALYSES

Individual and mean serum lebrizumab concentration ~~versus-time data~~ will be reported. *During the treatment period, M* mean concentrations will be reported at Weeks 4, 12, 24, 36, and 52 ($C_{\min, Wk4}$, $C_{\min, Wk12}$, $C_{\min, Wk24}$, $C_{\min, Wk36}$, C_{Wk52} , respectively). ~~The elimination half life will also be reported.~~ Estimates for these parameters will be tabulated and summarized (mean, SD, coefficient of variation, median, minimum, and maximum). Additional PK analyses during the treatment period or the 44-week safety follow-up period may be conducted as appropriate. Population PK modeling may be performed to characterize inter-individual variability, which may be reported separately from the clinical study report.

SECTION 6.8: OPTIONAL INTERIM ANALYSES

After the analysis of Cohort A, the Sponsor formed an IMC to perform an unplanned interim futility analysis of Cohort B to determine if it should be terminated for lack of sufficient efficacy. Following this analysis, the decision was made to continue the study and not perform additional efficacy and/or futility interim analyses.

SECTION 9.3: ADMINISTRATIVE STRUCTURE

This study is sponsored by F. Hoffmann-La Roche Ltd. ~~Approximately~~ A total of 120 international study centers ~~will have~~ participated in this study ~~to enrolling~~ ~~approximately 480~~ and enrolled 507 patients....

APPENDIX 1: Schedule of Assessments: Screening and Placebo Controlled Treatment Period – Cohort A

Appendix 1 has been revised and the row related to BodyMedia biosensor was removed.

APPENDIX 2: Schedule of Assessments: Open-Label Lebrikizumab Treatment Period – Cohort A

Appendix 2 has been revised and footnote l was amended as follows:

- ^l Includes IL-13 or IPF-related biomarkers (e.g., periostin, CCL18, YKL40, COMP, OPN, CCL13). ~~Screening serum periostin sample should be collected and shipped to the central laboratory within the first 2 weeks of screening.~~

APPENDIX 3: Schedule of Assessments: Screening, Pirfenidone Titration Run-In, and Placebo Controlled Treatment Period – Cohort B

Appendix 3 has been revised and footnote q was amended as follows:

- ^q On lebrikizumab dosing days. Samples for serum PK, PD, antibody (including anti-therapeutic antibody), and optional PAXgene mRNA analysis will be taken prior to lebrikizumab dosing. An additional sample for serum antibody and PK analysis must be taken in the event of an anaphylactic, anaphylactoid, or serious hypersensitivity reaction. *Anti*-PLB2 antibody testing may be performed as appropriate using serum samples collected at pre-specified timepoints.

APPENDIX 4: Schedule of Assessments: Safety Follow-Up Period

Appendix 4 has been revised and footnote k was amended as follows:

- ^k On lebrikizumab dosing days. Samples for serum PK, PD, antibody (including anti-therapeutic antibody), and optional PAXgene mRNA analysis will be taken prior to lebrikizumab dosing. An additional sample for serum antibody and PK analysis must be taken in the event of an anaphylactic, anaphylactoid, or serious hypersensitivity reaction. *Anti*-PLB2 antibody testing may be performed as appropriate using serum samples collected at pre-specified timepoints.

SAMPLE INFORMED CONSENT FORMS



The sample Informed Consent Forms have 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 IDIOPATHIC PULMONARY
FIBROSIS

PROTOCOL NUMBER: GB28547

VERSION NUMBER: 7

EUDRACT NUMBER: 2013-001163-24

IND NUMBER: 117,062

TEST PRODUCT: Lebrikizumab (RO5490255)

MEDICAL MONITORS: [REDACTED], M.D.
[REDACTED], M.D.

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. Please return a copy of the form as instructed by your local study monitor/Roche Affiliate.

PROTOCOL SYNOPSIS

TITLE: A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, STUDY TO ASSESS THE EFFICACY AND SAFETY OF LEBRIKIZUMAB IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS

PROTOCOL NUMBER: GB28547

VERSION NUMBER: 7

EUDRACT NUMBER: 2013-001163-24

IND NUMBER: 117,062

TEST PRODUCT: Lebrikizumab (RO5490255)

PHASE: II

INDICATION: Idiopathic Pulmonary Fibrosis

SPONSOR: F. Hoffmann-La Roche Ltd

Objectives

Efficacy Objectives

The primary efficacy objective for this study is to evaluate lebrikizumab compared with placebo as monotherapy or as combination therapy with pirfenidone background compared with placebo in patients with idiopathic pulmonary fibrosis (IPF), as measured by the *annualized rate of decline* in percentage of predicted forced vital capacity (FVC) *over 52 weeks*.

The secondary efficacy objectives are to evaluate lebrikizumab compared with placebo as monotherapy or as combination therapy with pirfenidone background therapy compared with placebo in patients with IPF as measured by:

- The efficacy on the basis of Progression Free Survival (PFS), pulmonary function, diffusion capacity, non-elective hospitalization for any cause, acute IPF exacerbation, *proportion of patients with at least 10% decline in percentage of predicted FVC or death, and all cause of death*
- The distance walked in 6 minutes and health-related quality of life questionnaires

Safety Objectives

The safety objectives for this study are the following:

- To evaluate the safety of lebrikizumab as monotherapy compared with placebo in patients with IPF
- To evaluate the safety of lebrikizumab with pirfenidone as background therapy compared with placebo with pirfenidone as background therapy in patients with IPF

Pharmacokinetic Objective

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

- To characterize the PK of lebrikizumab in patients with IPF

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To evaluate the efficacy of lebrikizumab compared with placebo as monotherapy or as combination therapy with pirfenidone compared with placebo in patients with IPF on the basis of changes in quantitative lung fibrosis (QLF) score on HRCT, *A Tool to Assess Quality of Life in IPF (ATAQ)*, and the BORG Category Ratio 10 Scale[®] (BORG CR10), and *time to first occurrence of St. George's Respiratory Questionnaire (SGRQ) individual domain worsening as defined by reaching minimal important difference (MID)*.
- To evaluate potential prognostic and predictive serum and whole blood RNA and DNA biomarkers associated with IPF

Study Design

Description of Study

This is a randomized, multicenter, double-blind, placebo-controlled, parallel-group study of lebrikizumab in patients with IPF. Approximately 480 patients with a diagnosis of IPF will be enrolled in the study across two cohorts (approximately 150 patients in Cohort A having approximately 75 patients per treatment arm and approximately 330 patients in Cohort B having approximately 165 patients per treatment arm) at approximately 120 sites located globally. The total treatment duration will be based on all patients receiving at least 13 doses (one dose every 4 weeks [Q4W]) of blinded treatment over 48 weeks. The study primary endpoint will measure the absolute change from baseline to Week 52 in percent predicted FVC.

Two cohorts of patients will be enrolled in the study; Cohort A patients will be treated in the absence of pirfenidone IPF background therapy; Cohort B patients will be treated with pirfenidone as background therapy.

Number of Patients

Approximately 480 patients with a diagnosis of IPF will be enrolled in the study across two cohorts (approximately 150 patients in Cohort A having approximately 75 patients per treatment arm and approximately 330 patients in Cohort B having approximately 165 patients per treatment arm) at approximately 120 sites located globally.

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 years at Visit 1
- Have a diagnosis of IPF based on the ATS/ERS/JRS/ALAT consensus statement on IPF within the previous 5 years from time of screening and confirmed at baseline.
- Have a central review assessment of an HRCT performed during the screening period or within 12 months prior to the start of screening.

All patients who have undergone a SLB as part of their initial workup should have pathology slides sent in for SLB central review assessment.

Eligibility will be determined on the basis of assessments in Table 1.

- A Multidisciplinary Discussion of Diagnosis (MDD) based on 2011 ATS/ERS/JRS/ALAT guidelines will be utilized to finalize the diagnosis in the event the initial central review outcome results for HRCT and SLB are disparate (inconsistent with UIP/definite UIP).

Additionally, patients must meet the following criteria for study entry:

- FVC $\geq 40\%$ and $\leq 100\%$ of predicted at screening
- Stable baseline lung function as evidenced by a difference of $< 10\%$ in FVC (L) measurements between screening and Day 1, Visit 2 prior to randomization
- Diffusion capacity of the lung for carbon monoxide (DL_{CO}) $\geq 25\%$ and $\leq 90\%$ of predicted at screening

- Ability to walk ≥ 100 meters unassisted in 6 minutes
- Cohort A: No background IPF therapy for ≥ 4 weeks allowed prior to randomization and throughout the placebo-controlled study period
- Cohort B: Tolerated dose of pirfenidone ≤ 2403 mg/QD for ≥ 4 weeks required prior to randomization and throughout the placebo-controlled study 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
- Evidence of other known causes of interstitial lung disease (ILD) (e.g., domestic and occupational environmental exposures, connective-tissue disease (CTD), and drug toxicity)
- Lung transplant expected within 12 months of screening
- Evidence of clinically significant lung disease other than IPF (e.g., asthma or chronic obstructive pulmonary disease [COPD])
- Post-bronchodilator forced expiratory volume in 1 second (FEV₁)/FVC ratio < 0.7 at screening
- Positive bronchodilator response evidenced by an increase of $\geq 12\%$ predicted and 200 mL increase in either FEV₁ or FVC
- Any clinically significant medical disease (other than IPF) that is associated with an expected survival of < 12 months, likely to require a change in therapy during the study, or likely to impact the ability of the patient to participate in the study in the opinion of the investigator, or impact the study efficacy or safety assessments
- Requirement for continuous medical care and assistance, or limited ability to self-care that would impact the ability of patient to participate in the study or to perform the study-related assessments
- Class IV New York Heart Association chronic heart failure or historical evidence of left ventricular ejection fraction $< 35\%$
- Hospitalization due to an exacerbation of IPF within 4 weeks prior to or during screening
- Known current malignancy or current evaluation for a potential malignancy
- Major episode of infection requiring any of the following:
 - Admission to the hospital for ≥ 24 hours within 4 weeks prior to screening or during screening and run-in period
 - Treatment with antibiotics (IV, IM, oral, or inhaled) within 4 weeks prior to screening or during screening and run-in period
- An active upper or lower respiratory tract infection occurring at any time within the screening period prior to the randomization visit (Visit 1 to Day 1, Visit 2)
- *Listeria monocytogenes* infection or active parasitic infection within 6 months prior to Day 1, Visit 2
- Active tuberculosis requiring treatment within 12 months prior to screening
- Known immunodeficiency, including but not limited to HIV infection
- Past 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
- 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 during screening
- Clinically significant abnormality on ECG at screening 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

- Receipt of a live/attenuated vaccine within the 4 weeks prior to Visit 1
- Chronic treatment with any of the following within 4 weeks or five half-lives prior to screening (whichever is longer) to the end of the placebo-controlled period (Day 365, Visit 16):
 - Immunosuppressive or immunomodulatory therapies (e.g., azathioprine, cyclosporine A, cyclophosphamide, D-penicillamine, interferon-gamma, tumor necrosis factor- α antagonists)
 - Cytotoxic drugs (e.g., colchicine) if used for IPF indication
 - Pirfenidone (Exclusion Limited to Cohort A)
 - N-acetylcysteine
 - Pulmonary hypertension therapies (e.g., endothelin receptor antagonist, phosphodiesterase type-5 inhibitor, riociguat, prostacyclin or prostacyclin analogue)
 - Tyrosine kinase inhibitors including exclusion of nintedanib for Cohort A and Cohort B
 - Warfarin or other anticoagulant therapy if given for IPF indication
 - Any unlicensed therapy given for IPF indication
 - Any investigational agent
- Chronic oral corticosteroid therapy is not permitted within 4 weeks prior to screening (Visit 1), during screening and run-in, *or throughout the study* period.
- History of alcohol, drug, or chemical abuse that would impair or risk the patient's full participation in the study, in the opinion of the investigator
- Female patients of reproductive potential who are not willing to use a highly effective method of contraception (e.g., contraceptive pill or transdermal patch, spermicide and barrier [i.e., condoms], intrauterine device, implants for contraception, injections for contraception [with prolonged release], hormonal vaginal device, sterilization, surgical tubal ligation) for the duration of the study and for at least 18 weeks after the last dose of lebrikizumab or placebo study treatment.
- Pregnant or lactating
- Body weight <40 kg

Additional exclusions that are limited to Cohort B (Pirfenidone Background):

- Known achalasia, esophageal stricture, or esophageal dysfunction sufficient to limit the ability to swallow oral medication
- Tobacco smoking or use of tobacco-related products within 3 months of screening or unwillingness to avoid smoking throughout the study (e.g., cigarette, pipe, cigar)
- Any condition that, as assessed by the investigator, might be significantly exacerbated by the known side effects associated with pirfenidone
- Known or suspected peptic ulcer
- Creatinine clearance < 40 mL/min, calculated using the Cockcroft-Gault formula
- Ongoing use or following therapies within 4 weeks of randomization (Day 1, Visit 2) or during the study
 - Strong inhibitors of CYP1A2 (e.g., fluvoxamine or enoxacin)
 - Moderate inducers of CYP1A2, limited to tobacco smoking and tobacco-related products

Length of Study

The total length of the study will be approximately 4 years from first patient screened to completion of the last patient visit. Individual patients may participate in the study for up to 2.9 years.

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 118 weeks after the last patient is enrolled and randomized into Cohort A. This timeframe includes a 52-week placebo-controlled period and a maximum of an additional 52 week open-label Lebrikizumab treatment period followed by the safety follow-up period. In the case that enrollment in Cohort B is slower than anticipated, LPLV is expected occur a maximum of 66 weeks after the last patient is enrolled and randomized into Cohort B. This timeframe includes a 52-weeks placebo-controlled period followed by the safety follow-up period. All patients will be followed for safety for 18 weeks after the last dose of study treatment of lebrikizumab or placebo by subcutaneous injection.

Outcome Measures

Efficacy Outcome Measures

The primary efficacy outcome measure for this study is the *annualized rate of decrease in percentage of predicted FVC over 52 weeks (% FVC/year)*.

Secondary Outcome Measures

The secondary efficacy outcome measures for this study are as follows:

- *Annualized rate of decline in 6-minute walk test (6MWT) distance over 52 weeks*
- *Time from randomization to first occurrence of a $\geq 10\%$ absolute decline in percentage of predicted FVC or death from any cause*
- *Annualized rate of decrease in percentage of predicted DL_{CO} over 52 weeks*
- *PFS, defined as the time from study treatment randomization to the first occurrence of any of the following disease progression or death events:*
 - *Death from any cause*
 - *All cause hospitalization*
 - *A decrease from baseline (relative change) of $\geq 10\%$ in FVC (mL/year)*
 - *Annualized rate of decrease in FVC over a 52-week period (mL/year)*
 - *Annualized rate of decrease in ATAQ-IPF total score over a 52-week period*
 - *Time from randomization to first occurrence of the SGRQ worsening (total score) as defined by reaching MID: Total Score = 7 or death from any cause*
 - *Time from randomization to non-elective hospitalization or death from any cause*
 - *Time from randomization to first event of acute IPF exacerbation as defined below*
 - *IPF exacerbation is defined as an event that meets all of the following criteria as determined by the investigator:*
 - *Unexplained worsening or development of dyspnea within the previous 30 days*
 - ***And** radiologic evidence of new bilateral ground-glass abnormality or consolidation superimposed on a reticular or honeycomb background pattern that is consistent with UIP*
 - ***And** absence of alternative causes, such as left heart failure, pulmonary embolism, pulmonary infection (on the basis of endotracheal aspirate or bronchoalveolar lavage, if available, or investigator judgment), or other events leading to acute lung injury (e.g., sepsis, aspiration, trauma, reperfusion pulmonary edema)*

Safety Outcome Measures

All safety outcome measures will be assessed by comparing results from the lebrikizumab treatment group with the placebo group. The safety outcome measures for this study are as follows:

- Frequency of adverse events during the study
- Severity of adverse events during the study
- Incidence of anti-therapeutic antibodies (ATAs) against lebrikizumab throughout the study

Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Serum lebrikizumab concentration at Week 52 (C_{Wk52})
- Predose serum lebrikizumab concentrations (C_{min}) at Weeks 4, 12, 24, and 36 ($C_{min,Wk4}$, $C_{min,Wk12}$, $C_{min,Wk24}$, and $C_{min,Wk36}$)
- Elimination half-life of lebrikizumab

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Change from baseline to Week 52 in radiographic findings on pulmonary HRCT, including QLF score
- *Change from screening (corresponding to timing for randomization strata) in serum and plasma biomarkers (e.g., periostin and CCL18) and change from baseline in serum and plasma biomarkers (e.g., periostin, chemokine (C-C motif) ligand 18 [CCL18], YKL40, COMP, OPN, CCL13)*
- Serum lebrikizumab concentrations during the extended treatment and the 14-week safety follow-up period
- Exposure-response relationships (to be evaluated as warranted)
- Change from baseline to Week 52 in the Borg CR10 Scale
- *Change from baseline to Week 52 in the ATAQ-IPF*
- *Time from randomization to first occurrence of SGRQ individual domain worsening as defined by reaching MID: Symptom = 8, Activity = 5, Impact = 7, or death from any cause*
- *Change from baseline to Week 52 in the SGRQ*

The analysis plan for the exploratory HRCT and biomarkers will be specified in a separate document.

Investigational Medicinal Products

Test Product

Lebrikizumab will be administered by subcutaneous injection of 250 mg every 4 weeks, with the first injection occurring at the randomization visit (Day 1, Visit 2). Patients will continue to receive blinded study treatment every 4 weeks during the placebo-controlled treatment period for a total of 13 doses/26 injections of blinded treatment.

Comparator

For patients in Cohort A, placebo will be administered. For patients in Cohort B, placebo plus a pirfenidone background dose of ≤ 2403 mg/d will be administered in divided doses three times per day with food.

Statistical Methods

Primary Analysis

The analysis of data from the placebo-controlled period *for each cohort* will be performed when all patients have either completed the *end of the placebo-controlled treatment (Week 52/EOT)* visit or discontinued early from the study. Treatment assignment will be unblinded to the personnel performing the analysis when all data through the EOT visit are in the database and the data have been cleaned and verified *for each cohort*.

The analysis of complete data for the study, including data from the placebo-controlled period, open-label extension period for Cohort A, and the 14-week safety follow-up period, will be performed when all patients have either completed the placebo-controlled period, open-label extension period for Cohort A, and 14-week safety follow-up period or discontinued early from the study, all data from the study are in the database, and the database is locked. *An interim futility analysis of Cohort B was conducted.*

Efficacy Analyses

The analysis of data from the treatment period in Cohort A will be performed when all patients enrolled in Cohort A have either completed the end of placebo controlled treatment visit (Week 52), or discontinued early from the study. Treatment assignment will be unblinded to the personnel performing the analysis when all data through the Week 52 visit are in the database and the data have been cleaned and verified.

The analysis of data from the treatment period in Cohort B will be performed when all patients enrolled in Cohort B have either completed the end of treatment visit (Week 52) or discontinued early from the study. Treatment assignment will be unblinded to the personnel performing the analysis when all data through the Week 52 visit are in the database and the data have been cleaned and verified.

However, the Sponsor study team directly involved in the study conduct (medical monitoring, clinical operations, drug safety, etc.) will not have access to individual treatment assignments until study completion, when all patients have completed the safety follow-up or discontinued the study. All non-Sponsor personnel who are involved in the conduct of the study (e.g., patients, site monitors, and investigators) will remain blinded to patient-specific treatment assignments until all patients complete the safety follow-up period or discontinue from the study. Complete details of the analysis will be provided in the SAP, which will be finalized prior to unblinding the data.

Safety Analyses

Safety analyses will be based on all patients who received at least one dose of *randomized* study drug, with patients grouped according to the actual treatment received. Safety summaries will be presented by treatment arm for all treated patients. *In addition, safety listings will be provided for any events reported during pirfenidone exposure prior to randomization.*

Safety will be assessed through the summary of adverse events, laboratory test results, (including antibodies to lebrikizumab), ECG, and vital signs. These summaries will be produced separately for *each cohort* for the treatment period (placebo-controlled study treatment period, the *Cohort A* open-label lebrikizumab period).

Pharmacokinetic Analyses

Individual and mean serum lebrikizumab concentration–versus-time data will be reported. *During the treatment period, mean concentrations will be reported at Weeks 4, 12, 24, 36, and 52 ($C_{min,Wk4}$, $C_{min,Wk12}$, $C_{min,Wk24}$, $C_{min,Wk36}$, C_{Wk52} , respectively). Estimates for these parameters will be tabulated and summarized (mean, SD, coefficient of variation, median, minimum, and maximum). Additional PK analyses during the treatment period or the safety follow-up period may be conducted as appropriate. Population PK modeling may be performed to characterize inter-individual variability, which may be reported separately from the clinical study report.*

Exploratory Analyses

Analysis of exploratory efficacy endpoints will be described in the Statistical Analysis Plan. Several pharmacodynamic biomarkers have been identified (e.g., periostin, CCL18, YKL40, COMP, OPN, CCL13) and will be measured in serum or plasma samples to assess the effect of lebrikizumab on these biomarkers. Exploratory exposure-response analysis will be performed as appropriate.

Determination of Sample Size

In Cohort A, a sample size of 75 patients in each treatment group will provide *approximately 80% power to detect a change in the annualized rate of decline in percentage of predicted FVC over 52 weeks of a 3.7% difference in the means of the absolute change from baseline in percentage of predicted FVC at 52 weeks, assuming that the common standard deviation is 8% (as reported in the placebo group in the ASCEND trial of pirfenidone) using a two group t-test with a 0.05 two-sided significance level.*

In Cohort B, a sample size of 165 patients in each treatment group will provide *approximately 80% power to detect a 2.5% difference in the annualized rate of decline in percentage of predicted FVC over 52 weeks, assuming that the common standard deviation is 8% (as reported in the ASCEND trial of pirfenidone) using a two group t-test with a 0.05 two-sided significance level.*

Optional Interim Analyses

The Sponsor may choose to conduct up to two interim efficacy analyses. Interim analyses will involve unblinding of treatment assignments to the Sponsor for purposes of data analysis and interpretation. Patients and all study site personnel will remain blinded to individual patient-level treatment assignments until completion of the trials. The decision to conduct optional interim analyses and the timing of the analyses will be documented in the Sponsor's trial master file prior to the conduct of the interim analyses. The interim analyses 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.

After the analysis of Cohort A, the Sponsor formed an IMC to perform an unplanned interim futility analysis of Cohort B to determine if it should be terminated for lack of sufficient efficacy. Following this analysis, the decision was made to continue the study and not perform additional efficacy and/or futility interim analyses.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
6MWT	6-minute walk test
ANA	anti-nuclear autoantibody
ATA	anti-therapeutic antibody
ATAQ-IPF	A Tool to Assess Quality of Life in Idiopathic Pulmonary Fibrosis
ATS/ERS/JRS/ALAT	American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association
Borg CR10 Scale	Borg Category Ratio 10 Scale [®]
CCL	chemokine (C-C motif) ligand
CCP	anti-citrullinated protein antibody
C _{min}	minimum serum concentration under steady-state conditions within a dosing interval
COPD	chronic obstructive pulmonary disease
CTD	connective-tissue disease
C _{Wk52}	serum concentration at Week 52
DL _{CO}	diffusion capacity of the lung for carbon monoxide
eCRF	electronic Case Report Form
EOT	end of treatment
EQ-5D	EuroQol 5-Dimension Questionnaire
FEV ₁	forced expiratory volume in 1 second
FVC	forced vital capacity
HRCT	high-resolution computed tomography
hulgG4	humanized monoclonal antibody
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMC	Internal Monitoring Committee
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IEC	independent Ethics Committee
IL	interleukin
IL-13R	interleukin 13 receptor
ILD	interstitial lung disease
IMP	investigational medicinal product
IPF	idiopathic pulmonary fibrosis
IRB	Institutional Review Board

Abbreviation	Definition
IV	intravenous
IxRS	interactive voice/Web response system
LPLV	last patient, last visit
MID	minimal important difference
MDD	Multidisciplinary Discussion of Diagnosis
PFS	progression-free survival
PK	pharmacokinetic
PRO	patient-reported outcome
QLF	quantitative lung fibrosis
Q4W	every 4 weeks
RCR	Roche Clinical Repository
SAP	Statistical Analysis Plan
SC	subcutaneous
SGRQ	St. George's Respiratory Questionnaire
RF	rheumatoid factor
SLB	surgical lung biopsy
SMT	Study Management Team
SpO2	oxygen saturation
SSc	scleroderma
UIP	usual interstitial pneumonitis
ULN	upper limit of normal
UTI	urinary tract infection

1. **BACKGROUND**

1.1 **BACKGROUND ON IDIOPATHIC PULMONARY FIBROSIS**

Idiopathic pulmonary fibrosis (IPF) is a specific form of fibrosing interstitial pneumonia limited to the lung and has the histopathologic pattern of usual interstitial pneumonia (UIP) upon analysis of a surgical lung biopsy. Historically, patients who receive a diagnosis of IPF required a surgical lung biopsy; however, the current definition allows for an IPF diagnosis through clinical and radiological methods ([Raghu et al. 2011](#)). The diagnosis of IPF requires the exclusion of other known causes of interstitial lung disease (ILD), such as domestic and occupational environmental exposures, connective-tissue disease, and drug toxicity ([Raghu et al. 2011](#)). Because it remains a diagnosis of exclusion, a detailed clinical assessment is required to exclude other diffuse parenchymal diseases.

Most patients are over 50 years of age and report an insidious onset of progressive dyspnea and non-productive cough over months to years. Inspiratory crackles are noted on examination of the chest, and finger clubbing is present in many patients. High-resolution computed tomography (HRCT) imaging shows bilateral peripheral-based reticular abnormalities, traction bronchiectasis, and honeycombing involving predominantly the lower lung zones. Pulmonary function assessment generally reveals reduced lung volumes with restrictive physiology, a diminished single-breath diffusing capacity, and hypoxemia with exercise.

Depending on the criteria used for identification of patients with IPF, an estimated 29,000 to 104,000 persons in the United States are diagnosed with IPF ([Raghu et al. 2006](#)). The European IPF network reports that there are probably 200,000 patients with IPF living in the European Union ([Nalysnyk et al. 2012](#)). The true prevalence of IPF worldwide is likely higher because most documented cases are advanced and under medical treatment, both likely to bias the sample away from detecting early disease ([Zeki et al. 2010](#)).

The clinical course of the disease is challenging to predict and patient rate of decline and progression to death is variable, with patient deterioration occurring rapidly, slowly, or with periods of stability interposed with acute decline ([Ley et al. 2011](#)). Some patients have gradual progression over years, followed by acute exacerbations associated with abrupt and often fatal hypoxemic respiratory failure ([Collard et al. 2007](#)). Spontaneous remissions do not occur with UIP, and 10-year survival is less than 15% ([Lynch and Belperio 2012](#)).

The most recent guidelines from the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (ATS/ERS/JRS/ALAT) joint task force for the diagnosis and management of IPF concluded that pharmacologic therapy for IPF is without definitive, proven benefit ([Raghu et al. 2011](#)).

At the time of publication of Protocol Version 3, there was no approved therapy in the United States for the treatment of IPF. As of October 2014, two oral therapies were approved by the FDA for treatment of IPF, pirfenidone (ESBRIET) and nintedanib (OFEV) with additional approval of nintedanib by European Commission (EC) in January 2015. Other commonly prescribed therapies *for IPF* including corticosteroid monotherapy, N-acetylcysteine, and combined corticosteroid (e.g., azathioprine or cyclophosphamide) therapy remain contraindicated ([Raghu et al. 2011](#)).

1.2 BACKGROUND ON LEBRIKIZUMAB

Lebrikizumab is a humanized monoclonal antibody (hulgG4) with a mutation in the hinge region for increased stability. Lebrikizumab binds specifically to soluble interleukin-13 (IL-13) with high affinity and neutralizes its functional activities with high potency.

Lebrikizumab does not bind to mouse IL-13, the commonly used species for animal models of IPF. Therefore, there are no nonclinical data available from in vivo lebrikizumab pharmacology/efficacy studies in animal models of IPF; however, numerous nonclinical studies supporting the use of other anti-IL-13 therapies have been published (see Section 1.3).

The nonclinical safety assessment of lebrikizumab includes results from eight completed in vitro and in vivo studies with a total of 160 cynomolgus monkeys exposed to lebrikizumab for up to 9 months. Lebrikizumab was well tolerated in single- and multiple-dose administration studies by intravenous (IV) and subcutaneous (SC) routes. The no observable adverse effect level for lebrikizumab in monkeys is considered to be 25 mg/kg given weekly by means of IV infusion or SC injection, and systemic exposure in the 9-month monkey toxicity study is at least 23-fold higher than the predicted exposure in humans with this dosing regimen.

Lebrikizumab has been investigated in ten completed clinical studies: five Phase I studies and five Phase II studies. In those studies, more than 700 individuals were exposed to at least one dose of lebrikizumab. This included 94 healthy volunteers, 18 patients with refractory Hodgkin's lymphoma, and more than 600 patients with asthma. The studies were designed to provide proof-of-concept data and to evaluate the safety, tolerability, and pharmacokinetic (PK) profile of lebrikizumab. Lebrikizumab has been well tolerated by patients in these clinical studies with varied levels of exposure.

In Phase I clinical studies, no consistent laboratory abnormalities, clinically significant ECG changes, or consistent changes in vital signs were observed. Phase II studies in asthma, a disease in which IL-13 also plays a key role ([Hershey 2003](#)), demonstrated that lebrikizumab significantly increases pulmonary function and potentially decreases the rate of acute exacerbations that require systemic corticosteroids ([Corren et al. 2011](#)). Pharmacodynamic evaluations in this and other studies provided evidence that lebrikizumab inhibits the activity of IL-13 supported by a reduction from baseline serum

levels of chemokines (chemokine ligand [CCL]13 and CCL17), IgE, and periostin. The biomarker serum periostin was evaluated in Study ILR4646g, and baseline serum periostin levels of $\geq 50\text{ng/mL}$ were shown to be predictive in patients who have a clinically meaningful benefit from lebrikizumab therapy.

The clinical data obtained to date from the Phase I and Phase II clinical studies supported an acceptable benefit-risk for continuing with the evaluation of lebrikizumab for the treatment of asthma. [REDACTED]

[REDACTED] Overall, no clinically important safety signals were consistently identified in the completed Phase II asthma studies. Injection-site reactions were reported in a greater proportion of lebrikizumab-treated patients, but these were all non-serious and in most cases did not require treatment. The injection-site reactions observed to date in ongoing and completed clinical trials have been consistent with the rate and severity of those reported with other biological SC injectable therapies.

Unblinded study results recently became available from three Phase III studies of patients with asthma, two Phase II studies of patients with atopic dermatitis and the current study of patients with IPF, which includes a placebo-controlled period for Cohort A. A total of 1798 patients were administered at least one dose of lebrikizumab in all these studies combined (1536 patients with asthma, 184 patients with atopic dermatitis, and 78 patients with IPF). [REDACTED]

[REDACTED] However, the safety profile of lebrikizumab in humans is not yet fully characterized by extensive experience with patient exposure. Therefore, the potential adverse effects and the likelihood of their occurrence cannot be fully known at this time. There will be continued careful monitoring of patients to collect this information throughout further clinical development, including studies in IPF.

See the Lebrikizumab Investigator's Brochure (IB) for details on nonclinical and clinical studies.

1.3 STUDY RATIONALE

IPF is characterized by varying degrees of interstitial fibrosis. Several extracellular matrix proteins including type I, III, and IV collagens, fibronectin, and tenascin-C are involved in the process of fibrosis in patients with IPF together with abnormal proliferation of mesenchymal cells, distortion of pulmonary architecture, and generation

of subepithelial fibroblastic foci. IL-13 and IL-4 are strong inducers of tissue fibrosis. In nonclinical models, transgenic overexpression of IL-13 in the lungs of mice is sufficient to induce collagen gene expression and profound subepithelial fibrosis (Zhu et al. 1999; Lee et al. 2001). Conversely, mice with targeted disruption of IL-13 and mice that are treated with blocking antibodies specific for IL-13 show reduced extracellular matrix deposition in bleomycin- and fluorescein isothiocyanate–induced pulmonary fibrosis models (Belperio et al. 2002; Kolodsick et al. 2004; Liu et al. 2004).

Multiple studies have concluded that expression and activity of IL-13 is elevated in patients with IPF. The expression of IL-13 and IL-13 receptors (IL-13Rs) IL-13R α 1 and IL-13R α 2 was found to be increased in lung biopsy samples from patients with IPF compared with normal controls, both at the messenger RNA and protein level (Jakubzick et al. 2004). IL-13 was also found to be elevated in the bronchoalveolar lavage fluid from patients with IPF compared with normal controls. Importantly, the level of IL-13 in these samples was negatively correlated with the key measures of lung function, percentage of predicted forced vital capacity (FVC), and diffusion capacity of the lung for carbon monoxide (DL_{CO}) (Park et al. 2009), suggesting pathogenic functions of IL-13 in patients with IPF.

In addition to IL-13 itself, serum biomarkers known to be expressed downstream from IL-13 signaling have also been shown to be elevated in patients with IPF. Periostin, an IL-13–inducible protein with a serum level that correlates with benefit from treatment with lebrikizumab in patients with asthma (Woodruff et al. 2007; Corren et al. 2011), is also elevated in the serum of patients with IPF (Okamoto et al. 2011; Naik et al. 2012). These elevated periostin levels have been shown to be negatively correlated with pulmonary function parameters (i.e., FVC and DL_{CO}) over a 6-month period (Okamoto et al. 2011). Periostin has been proposed to be a pathogenic factor in IPF on the basis of reduced bleomycin-induced pulmonary fibrosis observed in periostin-deficient mice, suggesting an additional mechanism by which IL-13 may contribute to disease (Uchida et al. 2012). IL-13 signaling also induces robust production of chemokine (C-C motif) ligand 18 (CCL18) from macrophages in vitro, and alveolar macrophages isolated from patients with IPF—but not from normal controls—constitutively express CCL18 protein (Prasse et al. 2006). Like periostin, CCL18 is increased in the serum of patients with IPF. CCL18 levels are reported to correlate with disease progression and prognosis, with patients who have higher levels of baseline CCL18 experiencing a greater decline in FVC and higher mortality rates (Prasse et al. 2007, 2009). Taken together, these data strongly suggest that IL-13 expression is elevated in patients with IPF and that signals from this cytokine to multiple fibrosis-relevant cell types play a key role in driving disease pathogenesis.

1.4 BENEFIT-RISK ASSESSMENT

IPF is characterized by progressive worsening of dyspnea and lung function and is associated with a poor prognosis (Raghu et al. 2011). Median survival following

diagnosis is 2 to 5 years (Cottin 2012). Two approved therapies are now available in the United States and Europe with the recent approval of ESBRIET and OFEV by the FDA and the EC in addition to the original approval of pirfenidone for IPF treatment in Japan. Both therapeutics provide similar effects on slowing the loss of lung function, measured as forced vital capacity percent (FVC)percentage of predicted; however, no benefit was achieved with respect to dyspnea, quality of life, or other clinically meaningful outcomes (King et al. 2014; Richeldi et al. 2014). Consequently, unmet medical need for this condition remains high, and a need remains to develop new treatments, such as lebrizumab, that may offer additional clinical benefit by interfering with a fibrotic pathway.

Given the evidence supporting a key role for IL-13 in disease pathogenesis, there is a compelling rationale to consider targeted anti-IL-13 therapy in patients with IPF.

The Sponsor unblinded the treatment assignment in Cohort A of the study in May 2016, and conducted the planned analysis of this placebo-controlled cohort to assess the benefit of lebrizumab monotherapy in accordance with this protocol. No clinically-meaningful treatment difference was observed between the lung function endpoints; however, the trends that were observed for the 6-minute walk test (6MWT) distance and A Tool to Assess Quality of Life in Idiopathic Pulmonary Fibrosis (ATAQ-IPF) were in favor of treatment with lebrizumab. There was no evidence of safety concerns in Cohort A and the cohort safety profile was generally consistent with the safety profile observed in previous asthma studies with lebrizumab.

The Sponsor performed an interim futility analysis for Cohort B in August 2016. Taken together, the Sponsor decided to continue the study for the Cohort A extension and Cohort B per the protocol.

At this time, the benefit-risk ratio supports the continuation of this Phase II study of lebrizumab in patients with IPF.

2. OBJECTIVES

2.1 EFFICACY OBJECTIVES

The primary efficacy objective for this study is to evaluate lebrizumab compared with placebo as monotherapy or as combination therapy with pirfenidone background compared with placebo in patients with IPF, as measured by the *annualized rate of decline* in percentage of predicted FVC *over 52 weeks*.

The secondary efficacy objectives are to evaluate lebrizumab compared with placebo as monotherapy or as combination therapy with pirfenidone background therapy compared with placebo in patients with IPF as measured by:

- The efficacy on the basis of PFS, pulmonary function, diffusion capacity, non-elective hospitalization for any cause, acute IPF exacerbation, *proportion of*

patients with at least 10% decline in percentage of predicted FVC or death, and all cause death

- The distance walked in 6 minutes and health-related quality of life questionnaires

2.2 SAFETY OBJECTIVES

The safety objectives for this study are the following:

- To evaluate the safety of lebrikizumab as monotherapy compared with placebo in patients with IPF
- To evaluate the safety of lebrikizumab with pirfenidone as background therapy compared with placebo with pirfenidone as background therapy in patients with IPF

2.3 PHARMACOKINETIC OBJECTIVE

The PK objective for this study is to characterize the pharmacokinetics of lebrikizumab in patients with IPF.

2.4 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To evaluate the efficacy of lebrikizumab compared with placebo as monotherapy or as combination therapy with pirfenidone compared with placebo in patients with IPF on the basis of changes in quantitative lung fibrosis (QLF) score on HRCT, *ATAQ*, and the BORG Category Ratio 10 Scale[®] (BORG CR10), and *time to first occurrence of the St. George's Respiratory Questionnaire (SGRQ) individual domain worsening as defined by reaching minimal important difference (MID; Swigris et al. 2010)*.
- To evaluate potential prognostic and predictive serum, and whole blood RNA and DNA biomarkers associated with IPF

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview of Study Design

This is a randomized, multicenter, double-blind, placebo-controlled, parallel-group study of lebrikizumab in patients with IPF. Approximately 480 patients with a diagnosis of IPF will be enrolled in the study across two cohorts (approximately 150 patients in Cohort A having approximately 75 patients per treatment arm and approximately 330 patients in Cohort B having approximately 165 patients per treatment arm) at approximately 120 sites located globally. The total treatment duration will be based on all patients receiving at least 13 doses (one dose every 4 weeks [Q4W]) of blinded treatment over 48 weeks. The study primary endpoint will measure the absolute change from baseline to Week 52 in percentage of predicted FVC.

Two cohorts of patients will be enrolled in the study; Cohort A patients will be treated in the absence of pirfenidone IPF background therapy; Cohort B patients will be treated with pirfenidone as background therapy.

Cohort A (monotherapy) approximately 150 patients will be randomized 1:1 to lebrikizumab (250 mg SC) every 4 weeks or placebo in the absence of background IPF therapy.

Cohort B (combination therapy) approximately 330 patients will be treated daily with the maximum tolerated dose of pirfenidone ≤ 2403 mg/d, and randomized 1:1 to either lebrikizumab (250 mg SC) every 4 weeks or placebo.

Patients who provide written informed consent will commence a screening period, which will last 28 days (± 14 days) to establish entry criteria. During the screening period, patients will have their IPF diagnosis (i.e., HRCT \pm surgical lung biopsy [SLB]) confirmed by central review based upon the 2011 ATS/ERS/JRS/ALAT guidelines.

For Cohort B/combination therapy, patients may initiate screening on a stable dose of pirfenidone or free of background IPF therapy. After completing the initial screening assessments ($28d \pm 14d$), eligible patients who are naive or not currently treated with pirfenidone will initiate the pirfenidone titration run-in period (4-6 weeks) with Visit 1.5 to allow for titration of pirfenidone to a dose of 2403/mg/d as per label (three 267 mg capsules three times a day [9 capsules daily] with food for a total of 2403 mg/day) or to the highest dose tolerated or recommended dose per country specific guidelines (see Section 4.3.4). Patients who are unable to complete the titration run-in period will be considered run-in failures.

At the end of the screening period, and applicable qualifying pirfenidone titration run-in period for patients requiring pirfenidone titration, eligible patients will be randomized in a 1:1 ratio within each cohort to double-blind treatment with SC lebrikizumab 250 mg or placebo. Dynamic hierarchical randomization will be performed centrally and stratified by region (United States, Europe/Canada, and other), lung function (FVC $< 50\%$, 50% to 75% , $> 75\%$ predicted), and serum periostin concentration (< 50 ng/mL, ≥ 50 ng/mL) in each cohort.

Study drug will be administered by SC injection every 4 weeks, with the first injection occurring at the randomization visit (Day 1, Visit 2). Patients will continue to receive blinded study treatment every 4 weeks during the placebo-controlled treatment period for a total of 13 doses/26 injections of blinded treatment. Safety, efficacy, and patient reported outcomes will be assessed throughout the placebo-controlled study period as detailed in the schedule of assessments (see [Appendix 1](#) and [Appendix 3](#)). The primary efficacy endpoint is the absolute change from baseline to Week 52 in percentage of predicted FVC.

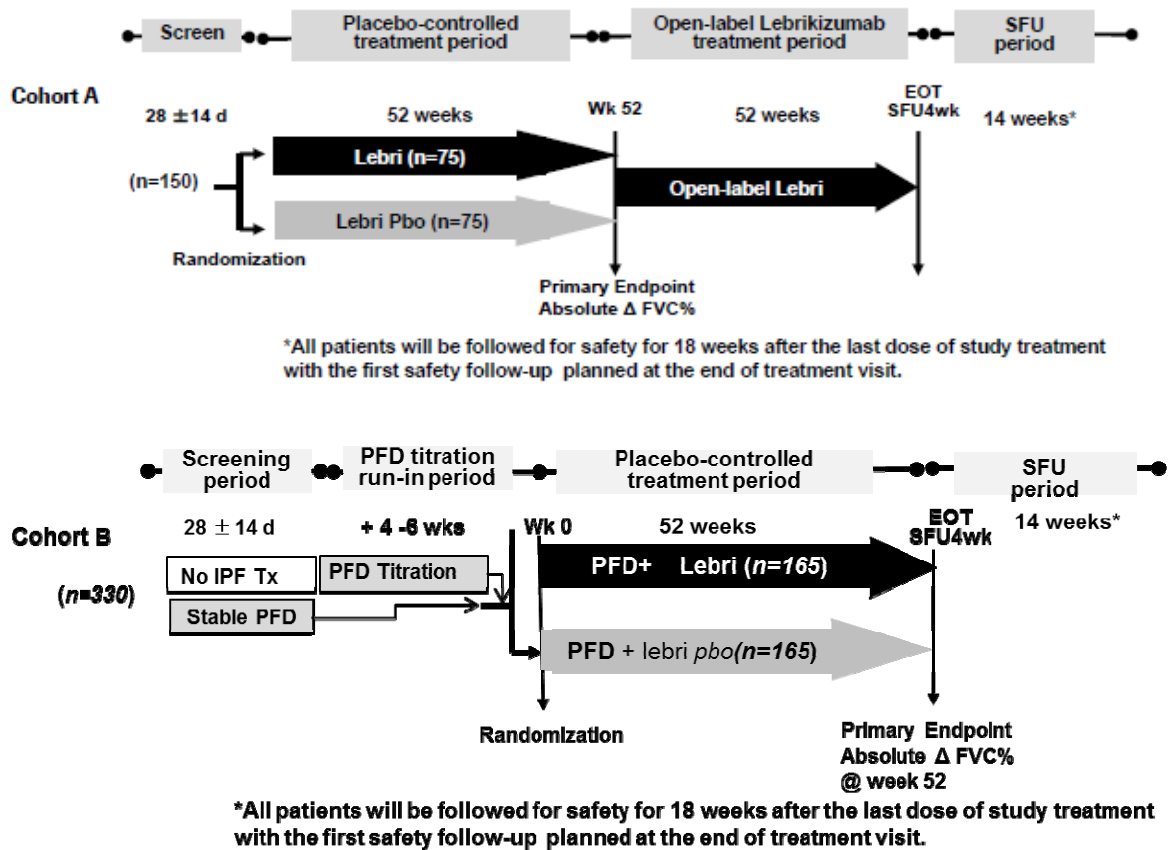
Patients in Cohort A who complete or exceed the minimum 52-week blinded placebo-controlled period (i.e., patients who have not prematurely discontinued study treatment) may continue into the 52-week open-label lebrikizumab treatment period. All patients who continue into the 52-week open-label lebrikizumab treatment period will receive SC lebrikizumab at a dose of 250 mg every 4 weeks. Exclusion of background IPF treatment is not required during this study period. During the open-label lebrikizumab period, at the investigator's discretion, a patient can start background therapy, including use of pirfenidone or other treatment, provided that it is an approved therapy for IPF in the applicable region (e.g., European Union, Canada, Mexico, Peru, or Japan) (see Section 4.4.1.2). Safety and efficacy will be measured as detailed in the schedule of assessments (see [Appendix 2](#)).

All patients will return to the clinic approximately 4 weeks after their last dose of study drug to complete follow-up assessments at the end-of-treatment (EOT) visit (see [Appendix 1](#), [Appendix 2](#), and [Appendix 3](#)). All patients will be followed-up for 18 weeks after the last dose including two subsequent visits during a 14-week safety follow-up period as indicated in schedule of assessments (see [Appendix 4](#)). Patients who choose to prematurely discontinue study drug will be encouraged to remain in the study and complete all remaining assessments. If this is not feasible, the patient should enter and complete the safety follow-up period unless consent has been withdrawn.

Measures of safety and efficacy will be assessed throughout the study as detailed in the schedule of assessments (see [Appendix 1](#), [Appendix 2](#), [Appendix 3](#), and [Appendix 4](#)). The primary efficacy outcome measure for this study is the absolute change from baseline to Week 52 in percentage of predicted FVC. A key secondary outcome will be PFS measured as the time from randomization to disease progression or death (see Section 2.2 and Section 3.3.1.1 for details). All other secondary and exploratory efficacy outcomes will be measured at Week 52 and at various other timepoints throughout the study.

A schedule of assessments is provided in [Appendix 1](#), [Appendix 2](#), [Appendix 3](#), and [Appendix 4](#) and a study schema is provided in [Figure 1](#).

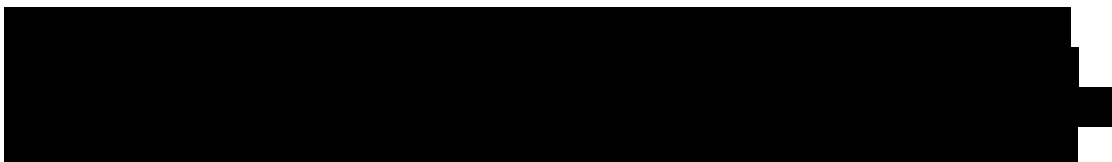
Figure 1 Study Schematic



3.1.2 Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will monitor safety and study conduct on an ongoing basis. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines the iDMC roles and responsibilities. The iDMC will meet approximately every 6 months to review unblinded safety and study conduct data provided by an independent Data Coordinating Center (iDCC). This will include a review of all deaths and hospitalizations reported on the adverse events forms. The study may be stopped early for safety reasons. If the iDMC determines that a benefit-risk assessment is necessary, the iDMC may also review unblinded efficacy data, although the iDMC may not recommend stopping the study for positive efficacy.

3.1.3 Internal Monitoring Committee



[REDACTED]

[REDACTED]

Details with regard to the IMC were documented in an IMC agreement.

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 118 weeks after the last patient is enrolled and randomized into Cohort A. This timeframe includes a 52-week placebo-controlled period and a maximum of an additional 52 week open-label lebrikizumab treatment period followed by the safety follow-up period. In the case that enrollment in Cohort B is slower than anticipated, LPLV is expected occur a maximum of 66 weeks after the last patient is enrolled and randomized into Cohort B. This timeframe includes a 52-weeks placebo-controlled period followed by the safety follow-up period. All patients will be followed for safety for 18 weeks after the last dose of study treatment of lebrikizumab or placebo by SC injection.

3.2.1 Rationale for Test Product Dosage

Lebrikizumab is a hulgG4 that inhibits IL-13 signaling. Both nonclinical and clinical data suggest that IL-13 signaling plays an important role in the pathogenesis of IPF (see Section 1.3). The mechanism of action of lebrikizumab is to block the interaction between IL-13 and its receptor and hence the intracellular signaling of IL-13. Because of the fast turnover of cytokines, it is hypothesized that optimal IL-13 blockade requires maintaining sustained concentrations of lebrikizumab in the lung. Assuming that IL-13 levels in the lung are in the range reported in the literature and the serum-to-lung ratio is 1:500 (Hart et al. 2001), a serum concentration of 10 µg/mL would be expected to maintain sufficiently high drug levels in the lung to neutralize IL-13. This target concentration is also consistent with the lower end of the observed Week 12 trough concentrations in the Phase II Study ILR4646g where lebrikizumab showed efficacy in reducing the rate of severe asthma exacerbations in patients whose asthma was uncontrolled despite inhaled corticosteroid therapy. Similar to asthmatics, patients with IPF have elevated levels of biomarkers associated with IL-13 biology, suggesting that the concentrations of lebrikizumab producing clinical benefit in asthma may also produce biological activity in IPF.

For the Phase II study in patients with IPF, a 250 mg Q4W dose was selected to maintain steady-state serum trough concentrations at or above this target concentration. Under the assumption that the pharmacokinetics of lebrikizumab in patients with IPF are similar to those in patients with asthma, this dose/regimen would be expected to maintain a mean steady-state trough concentration of approximately 30 µg/mL. Higher serum concentrations may be maintained in patients with IPF because less of the drug may partition into the lungs because of reduced microvascular supply in the damaged fibrotic lung tissue. In addition, a 3-fold higher concentration above the target allows for potentially faster clearance of lebrikizumab if autoantibodies are present (Dobashi et al. 2000; Magro and Crowson 2003; Feghali-Bostwick et al. 2007; Papiris et al. 2012). Selection of a 250-mg dose is also supported by the safety experience from previous asthma clinical studies.

Lebrikizumab is eliminated via typical IgG clearance pathways, including nonspecific endocytosis and catabolism to amino acid products, which do not involve CYP450 enzymes. Therefore, any direct drug-drug interaction with small molecule drugs, including pirfenidone, is unlikely. The PK of lebrikizumab in patients with IPF will be characterized in the Phase II study to ensure that the properties of the molecule in this indication are well understood.

3.2.2 Rationale for Pirfenidone Dosage

For patients in Cohort B, the background dose of pirfenidone will be ≤2403 mg/d administered in divided doses three times per day (TID) with food. Pirfenidone has been selected as background therapy for IPF based upon its broad approval by health authorities and availability throughout much of the world including in the 28 member states of the European Union, Japan, Canada, and United States. Pirfenidone (ESBRIET or PIRESPA) has been shown to slow the loss of lung function, measured as percentage of predicted FVC, in patients with IPF in three Phase III clinical trials. The summary of the safety data indicates that pirfenidone is generally well tolerated. The most common adverse events reported in Phase III trials were gastrointestinal disorders and skin disorders, typically mild to moderate, and could be managed by dose adjustment. In addition, the long term safety profile of pirfenidone has been well established with exposure in more than 1382 pirfenidone-treated patients from 14 clinical trials, (PFD IB) representing the experience from 2876 patient-exposure years and 519 patients with ≥2y exposure (some up to 10 years). The long-term safety profile was consistent with observations from Phase III clinical trials.

3.2.3 Rationale for Patient Population

IPF is a heterogeneous disease with variable progression characterized by deterioration of lung function. There is no established method of combining clinical or biomarker measures to accurately determine prognosis or define the stage of disease; therefore, the inclusion criteria have been set to include a broad population of patients with IPF. The study will target patients with a confirmed diagnosis of IPF consistent with the

diagnostic criteria published in the recent international ATS/ERS/JRS/ALAT guidelines (Raghu et al. 2011). Consistent with these guidelines, HRCT will be required to confirm the diagnosis of IPF and to exclude other possible causes of ILD in patients considered for enrolment. Surgical lung biopsies are not required for eligibility; however, those patients who have undergone such a procedure will have their slides adjudicated by central review to confirm eligibility in accordance with ATS/ERS/JRS/ALAT guidelines.

The inclusion criteria for this Phase II study were selected to allow patients with a broad spectrum of IPF disease the opportunity to participate, as reflected in the lung function (% FVC $\geq 40\%$ and $\leq 100\%$, % DL_{CO} $\geq 25\%$ and $\leq 90\%$), exercise capacity (6MWT ≥ 100 meters), and the length of time with disease (IPF diagnosis within previous 5 years of screening Visit 1) entry criteria. These parameters have been proposed to characterize disease severity and to identify patients who are likely to be influenced by the study intervention.

The primary objective of Study GB28547 is to evaluate lebrikizumab as monotherapy or in combination with pirfenidone background therapy compared with placebo in a Phase II study in patients with a confirmed diagnosis of IPF. Two cohorts of patients will be studied; **Cohort A** (patients with no IPF background medications) and **Cohort B** (patients who were treated with pirfenidone as background medication throughout the study period).

Eligibility in **Cohort A** excludes current use of pirfenidone and other approved, investigational, or other widely used therapies for IPF because of the potential confounding effects these therapies may have on the efficacy and safety analysis of lebrikizumab monotherapy. During the open-label lebrikizumab period, at the investigator's discretion, a patient can start background therapy, including use of pirfenidone or other treatment, provided that it is a therapy for IPF *approved* in the applicable region (e.g., European Union, Canada, Mexico, Peru, or Japan) (see Section 4.4.1.2).

Eligibility for **Cohort B** requires that all patients be on a maximum tolerated dose of pirfenidone ≤ 2403 mg/day as standard background therapy. A minimum of 4 weeks of exposure to pirfenidone is required prior to randomization, anticipating 52 weeks of background therapy. No other therapies may be used to treat IPF (see Section 4.4.1.2).

The Principal Investigator should notify the Medical Monitor of proposed changes in concomitant IPF therapy prior to starting rescue therapy *throughout the study for patients in either Cohort A or Cohort B*.

3.2.4 Rationale for Primary and Disease Response-Based Endpoints

In natural history settings of IPF, it is widely accepted that a decline in absolute FVC of 10% or more is a surrogate marker of mortality (Raghu et al. 2011), and in the absence

of an alternative explanation, disease progression. Smaller (5%–10%) but progressive, sustained declines in FVC may also represent disease progression ([Zappala et al. 2010](#)).

Changes over time in a patient's FVC (whether analyzed continuously or categorically above/below a threshold value) have been correlated with survival time in multiple large cohorts of patients with IPF ([Collard et al. 2007](#); [Flaherty et al. 2003](#); [du Bois 2011](#)).

Furthermore, the FDA approvals of pirfenidone and nintedanib were based upon similar measures of FVC: the change in percentage of predicted forced vital capacity (%FVC) from baseline to 52 weeks for pirfenidone and annual rate of decline in FVC. Patients treated with pirfenidone had a 4.5% treatment benefit relative to placebo treated patients and a modest improvement in survival (HR (95% HR [95% CI] = 0.75 [0.51-1.11]) (pirfenidone FDA label). Similar outcomes were observed in the OFEV trials (NEJM 2014 and product label).

The primary endpoint of this Phase II study will be the absolute change from baseline to Week 52 (end of treatment) in percentage of predicted FVC.

A key secondary endpoint in this study is PFS, which is defined as the time from study treatment randomization to the first occurrence of any one of the following events:

- Death from any cause
- Non-elective hospitalization for any cause
- Decrease from baseline of $\geq 10\%$ in FVC (L) (relative change)

The most clinically relevant domain of the proposed PFS endpoint is all-cause mortality ([du Bois 2010](#); [Papiris et al. 2012](#); [Raghu et al. 2012](#)). It is well defined, reliable, and easy to measure. All-cause mortality avoids losing clinically relevant information and inducing informative bias that occurs when deaths related to the study intervention are misclassified as “unrelated” and are censored. The all-cause mortality endpoint also captures potential off-target effects that could impact risk of mortality ([Raghu et al. 2012](#)).

Although it is commonly reported that the median survival time of those diagnosed with IPF is 3 to 5 years ([Cottin 2012](#)), the individual clinical course can be highly variable and unpredictable. In recent clinical trials the mortality rate in the placebo arms is consistently low highlighting that events of death are relatively rare in IPF trials ([Wells et al. 2012](#)). The current design combines all-cause mortality with additional parameters that have been shown to correlate with survival to increase the overall event rate.

The second PFS component, non-elective all-cause hospitalization, has validity in capturing disease progression leading to a decrease in patient health. Hospitalizations for those with IPF are often significant clinical events that carry a poor prognosis. The majority of hospitalizations in this population are respiratory related and correlates to cause of death, which is usually due to progressive fibrosis rather than

commonly occurring comorbidities (Martinez et al. 2005; Ley et al. 2011). Limitations of hospitalization endpoints include a variety of non-disease-related factors that can influence whether hospitalization occurs, such as access to health care, social support, and regional practice patterns, as well as the challenge of clinical data retrieval when a patient is hospitalized at a facility outside the study. Despite these limitations, non-elective hospitalization remains a clinically meaningful endpoint (Raghu et al. 2011). Similar to all-cause mortality, the all-cause hospitalization endpoint also captures potential off-target effects that could impact risk of hospitalization.

As stated above, it is widely accepted that a decline of 10% in a patient's FVC is a sign of disease progression and therefore a useful prognostic factor (Raghu et al. 2011). Using a relative (rather than absolute) change in FVC maximizes the chance of identifying a $\geq 10\%$ decline without sacrificing prognostic accuracy (Richeldi et al. 2011). Categorical decline of $\geq 10\%$ in FVC (relative) is the third PFS component.

3.2.5 Rationale for Control Group

A placebo-treated control group will be used in Cohort A of this study and a pirfenidone+placebo-treated control group will be used in Cohort B to assess the differences in pulmonary function, PFS, IPF-specific health-related quality of life, and safety in patients who receive lebrikizumab compared with patients who receive placebo. The use of a control group is necessary given the variability in the clinical course seen with different IPF cohorts in other clinical studies. Patients in the control group will undergo the same study assessments as the lebrikizumab-treated patients.

During the placebo-controlled periods, N-acetylcysteine or IPF therapy approved by local regulatory authorities can be initiated only after a confirmed progression event ($\geq 10\%$ decrease in FVC or non-elective hospitalization). No other therapies for IPF can be started at any time during the study.

For patients assigned to Cohort B, other approved therapies may be initiated in the absence of disease progression if pirfenidone is stopped because of safety considerations (see Section 4.4.1.2).

3.2.6 Rationale for Biomarker Assessments

The study will include a significant exploratory component focused on identification of biomarkers that may be prognostic for patients likely to have an accelerated rate of disease progression or diagnostic for identifying patients likely to benefit from treatment with lebrikizumab. Periostin is an IL-13-inducible protein with a serum level that correlates with benefit from treatment with lebrikizumab in patients with asthma (Woodruff et al. 2007; Corren et al. 2011). Periostin is also elevated in the serum of patients with IPF, and these levels have been shown to be negatively correlated with pulmonary function parameters (FVC and DL_{CO}) over a 6-month period (Okamoto et al. 2011; Naik et al. 2012). Periostin has been proposed to be a pathogenic factor in IPF on the basis of reduced bleomycin-induced pulmonary fibrosis observed

in periostin-deficient mice, suggesting an additional mechanism by which IL-13 may contribute to disease (Uchida et al. 2012).

Serum levels of periostin appear to have a distribution in patients with IPF similar to what has been observed in patients with asthma. Patients will be stratified across each treatment arm on the basis of periostin levels, tertiary to region, and baseline FVC. Patients with baseline periostin ≥ 50 ng/mL will be considered periostin high, and patients with baseline periostin < 50 ng/mL will be considered periostin low (Corren et al. 2011).

Serum and plasma samples will be collected during screening, at baseline and throughout the study, and at unscheduled visits to assess the relationship between periostin and other IL-13- and IPF-related biomarkers, disease progression, clinical status, and treatment benefit. Other IL-13- and IPF-related biomarkers that will be investigated may include but are not limited to CCL18, YKL40, COMP, OPN, CCL17, and CCL13. If novel IL-13- or IPF-related biomarkers are identified, they may be measured from stored serum or plasma.

3.3 OUTCOME MEASURES

3.3.1 Efficacy Outcome Measures

3.3.1.1 Primary Efficacy Outcome Measure

The primary efficacy outcome measure for this study is the *annualized rate of decrease in percentage of predicted FVC over 52 weeks (% FVC/year)*.

3.3.1.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are as follows:

- *Annualized rate of decline in 6MWT distance over 52 weeks*
- *Time from randomization to first occurrence of a $\geq 10\%$ absolute decline in percentage of predicted FVC or death from any cause*
- *Annualized rate of decrease in percentage of predicted DL_{CO} over 52 weeks*
- PFS, defined as the time from study treatment randomization to the first occurrence of any of the following *disease progression or death* events:
 - Death from any cause
 - All-cause hospitalization
 - A decrease from baseline (*relative change*) of $\geq 10\%$ in FVC (mL/year)
- *Annualized rate of decrease in FVC over a 52-week period (mL/year)*
- *Annualized rate of decrease in ATAQ-IPF total score over a 52-week period (see Appendix 5 for a description of the instrument)*
- *Time from randomization to first occurrence of the SGRQ (see Appendix 5 for a description of the questionnaire) worsening (total score) as defined by reaching MID (Swigris et al. 2010): Total Score = 7 or death from any cause*

- Time from randomization to non-elective hospitalization *or death from any cause*
- Time from randomization to first event of acute IPF exacerbation *as defined below:*

IPF exacerbation is defined as an event that meets all of the following criteria as determined by the investigator:

Unexplained worsening or development of dyspnea within the previous 30 days

***And** radiologic evidence of new bilateral ground-glass abnormality or consolidation superimposed on a reticular or honeycomb background pattern that is consistent with UIP*

***And** absence of alternative causes, such as left heart failure, pulmonary embolism, pulmonary infection (on the basis of endotracheal aspirate or bronchoalveolar lavage, if available, or investigator judgment), or other events leading to acute lung injury (e.g., sepsis, aspiration, trauma, reperfusion pulmonary edema)*

3.3.2 Safety Outcome Measures

All safety outcome measures will be assessed by comparing results from the lebrikizumab treatment group with the placebo group. The safety outcome measures for this study are as follows:

- Frequency of adverse events during the study
- Severity of adverse events during the study
- Incidence of anti-therapeutic antibodies (ATAs) against lebrikizumab throughout the study

3.3.3 Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Serum lebrikizumab concentration at Week 52 (C_{wk52})
- Predose serum lebrikizumab concentrations (C_{min}) at Weeks 4, 12, 24, and 36 ($C_{min,Wk4}$, $C_{min,Wk12}$, $C_{min,Wk24}$, and $C_{min,Wk36}$)
- Elimination half-life of lebrikizumab

3.3.4 Exploratory Outcome Measures

The exploratory outcome measures for this study include the following:

- Change from baseline to Week 52 in radiographic findings on pulmonary HRCT, including QLF score
- *Change from screening (corresponding to timing for randomization strata) in serum and plasma biomarkers (e.g., periostin and CCL18) and change from baseline in serum and plasma biomarkers (e.g., periostin, CCL18, YKL40, COMP, OPN, CCL13)*
- Serum lebrikizumab concentrations during the extended treatment and the 14-week safety follow-up period

- Exposure-response relationships (to be evaluated as warranted)
- Change from baseline to Week 52 in the Borg CR10 Scale
- *Change from baseline to Week 52 in the ATAQ-IPF*
- *Time from randomization to first occurrence of SGRQ individual domain worsening as defined by reaching MID (Swigris et al. 2010): Symptom =8, Activity =5, Impact =7, or death from any cause*
- *Change from baseline to Week 52 in the SGRQ*

The analysis plan for the exploratory HRCT and biomarkers will be specified in a separate document.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 480 patients ≥ 40 years of age who have a diagnosis of IPF *are* enrolled in this 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 years at Visit 1
- Have a diagnosis of IPF based on the ATS/ERS/JRS/ALAT consensus statement on IPF (Raghu et al. 2011) within the previous 5 years from time of screening and confirmed at baseline
- Have a central review assessment of an HRCT performed during the screening period or within 12 months prior to the start of screening.

All patients who have undergone an SLB as part of their initial workup should have pathology slides sent in for SLB central review assessment.

Eligibility will be determined on the basis of assessments in [Table 1](#).

- A Multidisciplinary Discussion of Diagnosis (MDD) based on 2011 ATS/ERS/JRS/ALAT guidelines will be utilized to finalize the diagnosis in the event the initial central review outcome results for HRCT and SLB are disparate (inconsistent with UIP/definite UIP).

Table 1 Combined High-Resolution Computed Tomography and Surgical Lung Biopsy Eligibility Assessment

HRCT Assessment	Surgical Lung Biopsy Assessment					
	Definite UIP	Probable UIP	Possible UIP	Non-Classifiable Fibrosis	Inconsistent with UIP	No SLB
Definite UIP	Eligible	Eligible	Eligible	Eligible	Not eligible	Eligible
Possible UIP	Eligible	Eligible	Eligible	Eligible	Not eligible	Eligible
Inconsistent with UIP	May be eligible/MDD	Not eligible	Not eligible	Not eligible	Not eligible	Not eligible

HRCT = high-resolution computed tomography; MDD = Multidisciplinary Discussion of Diagnosis; SLB = surgical lung biopsy; UIP = usual interstitial pneumonia.

Additionally, patients must meet the following criteria for study entry:

- FVC $\geq 40\%$ and $\leq 100\%$ of predicted at screening
- Stable baseline lung function as evidenced by a difference of $< 10\%$ in FVC (L) measurements between screening and Day 1, Visit 2 prior to randomization
- DL_{CO} $\geq 25\%$ and $\leq 90\%$ of predicted at screening
- Ability to walk ≥ 100 meters unassisted in 6 minutes
- Cohort A: No background IPF therapy for ≥ 4 weeks allowed prior to randomization and throughout the placebo-controlled study period
- Cohort B: Tolerated dose of pirfenidone ≤ 2403 mg/QD for ≥ 4 weeks required prior to randomization and throughout the placebo-controlled study period

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
- Evidence of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective-tissue disease [CTD], and drug toxicity)
- Lung transplant expected within 12 months of screening
- Evidence of clinically significant lung disease other than IPF (e.g., asthma or COPD)
- Post-bronchodilator forced expiratory volume in 1 second (FEV₁)/FVC ratio < 0.7 at screening
- Positive bronchodilator response evidenced by an increase of $\geq 12\%$ predicted and 200 mL increase in either FEV₁ or FVC

- Any clinically significant medical disease (other than IPF) that is associated with an expected survival of < 12 months, likely to require a change in therapy during the study, or likely to impact the ability of the patient to participate in the study in the opinion of the investigator, or impact the study efficacy or safety assessments
- Requirement for continuous medical care and assistance or limited ability to self-care that would impact the ability of patient to participate in the study or to perform the study-related assessments
- Class IV New York Heart Association chronic heart failure or historical evidence of left ventricular ejection fraction < 35%
- Hospitalization due to an exacerbation of IPF within 4 weeks prior to or during screening
- Known current malignancy or current evaluation for a potential malignancy
- Major episode of infection requiring any of the following:
 - Admission to the hospital for ≥ 24 hours within 4 weeks prior to screening or during screening and run-in period
 - Treatment with antibiotics (IV, IM, oral, or inhaled) within 4 weeks prior to screening or during screening and run-in period
- An active upper or lower respiratory tract infection occurring at any time within the screening period prior to the randomization visit (Visit 1 to Day 1, Visit 2)
- *Listeria monocytogenes* infection or active parasitic infection within 6 months prior to Day 1, Visit 2
- Active tuberculosis requiring treatment within 12 months prior to screening
- Known immunodeficiency, including but not limited to HIV infection
- Past 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
- 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 during screening
- Clinically significant abnormality on ECG at screening 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
- Receipt of a live/attenuated vaccine within the 4 weeks prior to Visit 1
- Chronic treatment with any of the following within 4 weeks or five half-lives prior to screening (whichever is longer) to the end of the placebo-controlled period (Day 365, Visit 16):
 - Immunosuppressive or immunomodulatory therapies (e.g., azathioprine, cyclosporine A, cyclophosphamide, D-penicillamine, interferon-gamma, tumor necrosis factor- α antagonists)

Cytotoxic drugs (e.g., colchicine) if used for IPF indication

Pirfenidone (Exclusion Limited to Cohort A)

N-acetylcysteine

Pulmonary hypertension therapies (e.g., endothelin receptor antagonist, phosphodiesterase type-5 inhibitor, riociguat, prostacyclin or prostacyclin analogue)

Tyrosine kinase inhibitors including exclusion of nintedanib for Cohort A and Cohort B

Warfarin or other anticoagulant therapy if given for IPF indication

Any unlicensed therapy given for the indication of IPF

Any investigational agent

- Chronic oral corticosteroid therapy is not permitted within 4 weeks prior to screening (Visit 1), during screening and run-in, *or throughout the study* period
- History of alcohol, drug, or chemical abuse that would impair or risk the patient's full participation in the study, in the opinion of the investigator
- Female patients of reproductive potential who are not willing to use a highly effective method of contraception (e.g., contraceptive pill or transdermal patch, spermicide and barrier [i.e., condoms], intrauterine device, implants for contraception, injections for contraception [with prolonged release], hormonal vaginal device, sterilization, surgical tubal ligation) for the duration of the study and for at least 18 weeks after the last dose of lebrikizumab or placebo study treatment) (see [Appendix 9](#))
- Pregnant or lactating
- Body weight < 40 kg

4.1.2.1 Additional Exclusions Limited to Cohort B (Pirfenidone Background)

- Known achalasia, esophageal stricture, or esophageal dysfunction sufficient to limit the ability to swallow oral medication
- Tobacco smoking or use of tobacco-related products within 3 months of screening or unwillingness to avoid smoking throughout the study (e.g., cigarette, pipe, cigar)
- Any condition that, as assessed by the investigator, might be significantly exacerbated by the known side effects associated with pirfenidone
- Known or suspected peptic ulcer
- Creatinine clearance < 40 mL/min, calculated using the Cockcroft-Gault formula
- Ongoing use of the following therapies or agents within 4 weeks of randomization (Day 1, Visit 2), or during the study

Strong inhibitors of CYP1A2 (e.g., fluvoxamine or enoxacin)

Moderate inducers of CYP1A2, limited to tobacco smoking and tobacco-related products

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 on Day 1, patients will be assigned an identification number (a different number from the screening number) and will be randomized in a 1:1 ratio to one of two treatment arms (**Cohort A** - lebrikizumab 250 mg SC or placebo SC every 4 weeks; **Cohort B** - lebrikizumab 250 mg SC and pirfenidone \leq 2403 mg/d or placebo SC every 4 weeks and pirfenidone \leq 2403 mg/d) for the 52-week placebo-controlled study period. Patients will be randomized on the same day that treatment is to be initiated (Day 1, Visit 2). Dynamic hierarchical randomization will be performed centrally and stratified by region (United States, Europe/Canada, other), lung function (FVC $<$ 50%, 50% to 75%, $>$ 75% predicted), and serum periostin concentration ($<$ 50 ng/mL, \geq 50 ng/mL) within each cohort. During the placebo-controlled study period and the open-label lebrikizumab treatment period, the IxRS will make study treatment kit assignments. IxRS will also make pirfenidone treatment kits available for patients in Cohort B. At each dosing visit during the placebo-controlled period, study treatment kits will be assigned for administration. The placebo and active kits are filled and packaged to look identical. Patient randomization and the study treatment kit assignments will be verified on an ongoing basis by an external and independent statistical coordinating center to ensure that randomization and kit assignments are conducted correctly by the IxRS.

Patients, all study site personnel, and the Sponsor and its agents (with the exception of the IxRS service provider, the external independent statistical coordinating center responsible for verifying patient randomization and study treatment kit assignments, PK/PD laboratory personnel, the iDMC and iDCC members) will be blinded to treatment assignment throughout the placebo-controlled period. As described in Section 6, treatment assignment will be unblinded to the personnel performing the analysis when all data for the primary endpoint period are in the database and the data have been cleaned and verified. [REDACTED]

[REDACTED] However, patients and all study site personnel will remain blinded to 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.

If unblinding is necessary for patient management (in the case of a serious adverse event), 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 treatment 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 or 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

[REDACTED]

For further details, see the Lebrikizumab IB.

4.3.2 Pirfenidone/Background Treatment in Cohort B

ESBRIET (pirfenidone) is approved in a 267-mg capsule dosage form. The recommended dose is 801 mg (i.e., three 267-mg capsules) TID, at the same times each day, taken with food (total dose, 2403 mg/d) (Section 4.3.4). ESBRIET is packaged in a 250-cc HDPE bottle. For information on the formulation, packaging, and handling of pirfenidone see the local prescribing information for ESBRIET or PIRESPA in Japan or the pirfenidone IB. For patients treated with PIRESPA (limited to Japan), dose titration and management of adverse effects should be based upon guidance in the marketed product label including a maximum recommended dose ≤ 1800 mg/d. Investigators are advised to follow the country specific guidance for dose titration and handling.

Pirfenidone, licensed as ESBRIET or PIRESPA, may be locally sourced for patients with access through their healthcare provider until it is provided by the Sponsor as IMP through the IxRS system.

4.3.3 Dosage, Administration, and Compliance

4.3.3.1 Lebrikizumab and Placebo (Cohort A)

Patients in Cohort A and Cohort B who meet all eligibility criteria will be randomly assigned to receive lebrikizumab 250 mg or placebo Q4W for the 52-week placebo controlled period.

Treatment with lebrikizumab or placebo will be by SC injection in the arm, thigh, or abdomen. All patients will receive a total of two injections per dosing visit. Each injection should be administered in a separate location at least 10 cm from the other injection site at each dosing visit. Study sites will be asked to record each injection site. Patients will be monitored for a minimum of 1 hour after dosing for the first three treatment visits and for 30 minutes for all subsequent treatment visits. Each patient will receive a minimum of 13 doses (2 injections per dose) of study treatment during the placebo-controlled, blinded, study treatment period. Patients in Cohort A who enrolled in the study prior to this amendment may receive up to 31 doses of blinded study treatment based upon previous version of this protocol. No dosage modification is permitted during the study.

Patients in **Cohort A** will receive an additional 52 weeks of open-label lebrikizumab (13 doses) in the open-label lebrikizumab treatment period after completion of the placebo controlled period.

4.3.4 Pirfenidone Background Treatment

The recommended dose of pirfenidone is 2403 mg/d (or 1800 mg/d for patients in Japan) administered in divided doses three times per day (TID) with food. Initial pirfenidone treatment should be titrated over 14 days, as tolerated, to the full dose of 9 capsules per day (three capsules TID), as follows:

- Days 1–7: one capsule TID
- Days 8–14: two capsules TID
- Day 15 and continuing: three capsules TID (maximum of 9 capsules daily)

Each dose should be taken with food, at approximately the same times each day. Patients will remain on a stable maintenance dose for the duration of the study period unless the dose is reduced to manage an AE. All doses of pirfenidone are to be taken with food to reduce the likelihood of gastrointestinal symptoms. The dose titration period of 14 days at the initiation of treatment is designed to maximize tolerability. Exposure to sunlight (including sunlamps and tanning beds) should be avoided to minimize the possibility of photosensitivity reactions or rash. Patients should be instructed to use sunscreens that have a sun protection factor (SPF) of 50 or higher as well as protection against ultraviolet A (UV-A) and ultraviolet B (UV-B) radiation. Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.4. For patients treated with PIRESPA (limited to Japan), dose titration and management of

adverse effects should be based upon guidance in the marketed product label including a maximum recommended dose ≤ 1800 mg/d (Costabel et al. 2014).

If a patient experiences significant side effects, treatment of symptoms and/or temporary dose modifications should be considered. The decision to modify pirfenidone dosing is ultimately the responsibility of the investigator; however, occasional day-to-day variability in dosing due to patient initiative and preference is expected to occur.

Patients who enter the pirfenidone titration run-in period will be monitored for a minimum of 4 weeks and up to 6 weeks after screening and prior to randomization, to allow for dose modifications due to tolerability issues and to limit the requirement for dose adjustment during the 52-week study period.

Any overdose or incorrect administration of pirfenidone should be noted on the pirfenidone administration eCRF. Adverse events associated with either an overdose or incorrect administration of pirfenidone should be recorded on the Adverse Event eCRF.

4.3.5 Investigational Medicinal Product Accountability

The investigational medicinal product (IMP) required for completion of this study (i.e., lebrikizumab and pirfenidone) will be provided by the Sponsor. Pirfenidone, licensed as ESBRIET or PIRESPA, may be locally sourced for patients with access through their healthcare provider until provided by the Sponsor as IMP through the IxRs system. The investigational site will acknowledge receipt of the IMP, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

The IMP will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon 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 IMP received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.6 Post-Study Access to Lebrikizumab and Pirfenidone

The Sponsor will offer post-study access to the study drug lebrikizumab and/or pirfenidone free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study drug after the end of the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being

- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any applicable legal or regulatory requirements

A patient will not be eligible to receive study drug after the end of the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or would not otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for IPF
- The Sponsor has reasonable safety concerns about the study drug as treatment for IPF
- Provision of study drug is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following location:

http://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/global_standards.htm.

4.4 CONCOMITANT THERAPY

4.4.1 Permitted Therapy

Concomitant therapy is defined as any medication (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, and nutritional supplements) used by a patient from 7 days prior to screening to the study completion/early termination visit. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF).

4.4.1.1 Corticosteroids

Chronic maintenance oral corticosteroid therapy, defined as daily or alternate day oral corticosteroid maintenance therapy is not permitted within the 4 weeks prior to screening Visit 1, during screening *and run-in*, or throughout the study period. Short-term treatment with corticosteroids (≤ 4 weeks) with subsequent corticosteroid dose tapering is permitted for patients who experience an acute IPF exacerbation as defined in Section 4.5.12.

4.4.1.2 Rescue Therapy

Patients in Cohort A who experience confirmed disease progression ($\geq 10\%$ decline in FVC [*mL/year; relative change*] or non-elective hospitalization) during the placebo-controlled study period will be allowed, at the investigator's discretion, to start rescue therapy, including use of pirfenidone or other IPF treatment provided that it is a therapy for IPF *approved* in the applicable region (e.g., European Union, Canada,

Mexico, Peru, or Japan). Patients who start rescue therapy will be allowed and encouraged to remain in the study and continue study treatment.

During the open-label lebrikizumab study period, at the investigator's discretion, a patient can initiate additional therapy for IPF that is approved in the applicable region (e.g., European Union, Canada, Mexico, Peru, or Japan) without evidence of disease progression.

Patients in Cohort B who experience a confirmed disease progression ($\geq 10\%$ decline in FVC [*mL/Year; relative change*] or non-elective hospitalization) during the placebo controlled study period should continue the study drug medication, including background pirfenidone. However, at the investigator's discretion, the initiation of rescue therapy that is approved by local regulatory authorities is allowed. Combination treatment with pirfenidone and nintedanib is not permitted throughout the study, given lack of adequate safety information on this drug combination. *Patients in Cohort B may initiate other approved therapies in the absence of disease progression if pirfenidone is stopped because of safety considerations.* The Principal Investigator should notify the Medical Monitor of proposed changes in concomitant IPF therapy prior to starting rescue therapy for patients in either Cohort A or Cohort B throughout the study.

Patients who start rescue therapy must begin appropriate monitoring per the prescribing information for that therapy. All safety laboratory assessments, including those required for the prescribed rescue medication, should be analyzed by the central laboratory utilized for the GB28547 clinical study.

4.4.2 Prohibited Therapy

- Chronic treatment with any of the following within 4 weeks or five half-lives prior to screening (whichever is longer) to the end of the placebo-controlled period (Day 365, Visit 16)
 - Immunosuppressive or immunomodulatory therapies (e.g., azathioprine, cyclosporine A, cyclophosphamide, D-penicillamine, interferon-gamma, tumor necrosis factor- α antagonists)
 - Cytotoxic drugs (e.g., colchicine) if used for IPF indication
 - Pirfenidone (exclusion limited to Cohort A)
 - N-acetylcysteine
 - Pulmonary hypertension therapies (e.g., endothelin receptor antagonist, phosphodiesterase type-5 inhibitor, riociguat, prostacyclin, or prostacyclin analogue)
 - Tyrosine kinase inhibitors including nintedanib for Cohort A and Cohort B
 - Warfarin or other anticoagulant therapy if given for IPF indication
 - Any unlicensed therapy given for the indication of IPF
 - Any investigational agent

- Chronic oral corticosteroid therapy is not permitted within 4 weeks prior to screening (Visit 1), during screening and *run-in*, or throughout the study period.
- N-acetylcysteine or IPF therapy approved by local regulatory authorities can be initiated in the event of disease progression as per Section 4.4.1.2. *Patients in Cohort B may initiate other approved IPF therapies in the absence of disease progression if pirfenidone is stopped because of safety considerations.*
- No other therapies for IPF can be started at any time during the study.

4.4.2.1 Prohibited Therapy Limited to Cohort B (Background Pirfenidone)

- Ongoing use of the following therapies or agents within 4 weeks of randomization (Day 1, Visit 2) or *at the initiation of pirfenidone (whichever is longer) to the end of the safety follow-up period*

Strong inhibitors of CYP1A2 (e.g., fluvoxamine or enoxacin)

Moderate inducers of CYP1A2 limited to tobacco smoking and tobacco-related products

- Concomitant administration of ESBRIET and ciprofloxacin (a moderate inhibitor of CYP1A2) moderately increases exposure to ESBRIET. If ciprofloxacin at the dosage of 750 mg twice daily cannot be avoided, reduce ESBRIET to two capsules three times a day, per ESBRIET package insert instructions. Monitor patients closely when ciprofloxacin is used at a dosage of 250 mg or 500 mg once daily.

4.5 STUDY ASSESSMENTS

4.5.1 Description of Study Assessments

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), inflammatory/autoimmune disease, smoking history, use of alcohol and drugs of abuse within the previous year, and specified conditions pre-set on the Targeted Medical History such as pulmonary hypertension, familial IPF, gastroesophageal reflux disease. These conditions should all be addressed on the Targeted Medical History and Baseline Conditions Log eCRF. All other medical history conditions, including any histories of alcoholism or drug abuse (except for smoking history and prior and concomitant surgeries and procedures, would be entered on the General Medical History and Baseline Conditions Log eCRF. Any history of smoking should be entered on the Tobacco Use History eCRF.

All concomitant medications (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by the patient within 90 days prior to Screening/Visit 1 should be entered on the Concomitant Medications log eCRF. A start date should be entered for all medication items entered on the Concomitant Medications eCRF, including those medications used chronically.

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

4.5.3 Physical Examinations

A complete physical examination should include the following: an evaluation of the head, eyes, ears, nose, throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. No rectal or pelvic examination is required. 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. Changes from baseline abnormalities should be recorded in patient notes. New or worsened abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs, Resting Pulse Oximetry, Weight, and Height

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Pulse oximetry should be measured while resting. Weight and height will also be measured at designated intervals (see [Appendix 1](#), [Appendix 2](#), [Appendix 3](#), and [Appendix 4](#)).

4.5.5 Spirometry

Spirometry, including the procedure for bronchodilator testing, will be conducted as per the study Pulmonary Function Manual, which is based on the ATS/ERS Consensus Statement ([Miller et al. 2005](#)). The manual will include information on equipment, procedures, patient instructions, and precautions. Spirometry will be performed on a centralized spirometry system (provided to all sites by the spirometry vendor) configured to the requirements of the study and in accordance with ATS/ERS guidelines.

Spirometric measures to be collected will include FEV₁ and FVC values as well as flow-volume and volume-time curves. The National Health and Nutrition Examination Survey (NHANES) III dataset as described by Hankinson and colleagues ([1999](#)) will be used to calculate percent-predicted FEV₁ and FVC values. The NHANES data sets have been standardized on the basis of key demographic information that includes ethnicity and race. It is therefore necessary to collect patient race/ethnicity to ensure that the most appropriate reference equation is used to establish the predicted values.

Acceptability of the spirometry data from the computerized configured system, including the graphic representations of the maneuvers, will be determined by over-readers blinded to study drug treatment. Calculations for the reproducibility of the acceptable maneuvers will be performed and reviewed centrally by over-readers blinded to study drug treatment and/or the Medical Monitor.

Patients must be aware that medications containing bronchodilators may affect spirometry and must be withheld until assessments are completed on the day of the study visits. The last dose of short-acting beta-agonists must be at least 4 hours

before testing and the last dose of long-acting beta-agonists must be at least 12 hours prior to testing.

Pre-bronchodilator and post-bronchodilator spirometry will be assessed during screening and at subsequent visits according to the schedules of assessments in [Appendix 1](#), [Appendix 2](#), [Appendix 3](#), and [Appendix 4](#).

4.5.6 Gas Exchange-Diffusion Capacity of the Lung for Carbon Monoxide Assessment

DL_{CO} will be conducted as per the study Pulmonary Function Manual, which is based on the 2005 ATS/ERS Consensus Statement ([MacIntyre et al. 2005](#)). DL_{CO} measurements corrected for serum hemoglobin concentration will be used for determining eligibility and endpoint assessments. DL_{CO} testing will be performed on a centralized DL_{CO}/spirometry system (provided to all sites by the spirometry vendor) configured to the requirements of the study and in accordance with ATS/ERS guidelines. The acceptability of the data, including the graphic representations of the maneuvers, will be determined by over-readers blinded to study drug treatment. Calculations for the reproducibility of the acceptable maneuvers will be performed and reviewed centrally.

4.5.7 High-Resolution Computed Tomography

Pulmonary HRCT scans will be obtained during screening to confirm the IPF diagnosis. Good-quality standard-of-care scans obtained ≤ 12 months prior to screening and in accordance with study image acquisition guidelines can be used for eligibility determination. HRCT scans will be reviewed first by the site radiologist and/or investigator to assess for eligibility. If the site determines that the patient's HRCT meets IPF diagnostic criteria as specified in [Table 1](#), the HRCT scans will be sent for central review to confirm eligibility. The blinded central review radiologist will evaluate screening images for the UIP Pattern (Definite UIP, Possible UIP, or Inconsistent with UIP) in accordance with the 2011 ATS/ERS/JRS/ALAT Statement ([Raghu et al. 2011](#)). The HRCT assessment criteria are outlined in [Appendix 10](#). Final eligibility will be determined by the central review assessments inclusive of SLB when available. An MDD based on 2011 ATS/ERS/JRS/ALAT guidelines will be utilized to finalize the diagnosis in the event the initial central review outcome results for HRCT and SLB are disparate (inconsistent with UIP/definite UIP). The MDD process will be managed by the imaging vendor, who will coordinate review with an external pulmonologist expert and manage the services of the same external pulmonologist with regards to the management of IPF in addition to the study radiologist and pathologist.

4.5.8 Optional Quantitative High-Resolution Computed Tomography Scan

An optional follow-up pulmonary HRCT scan will be obtained at Week 52 from consenting patients to evaluate for changes in quantitative HRCT fibrosis scores. The optional HRCT scan will be offered to randomized patients in the United States.

A written informed consent from each individual who has opted in to the optional quantitative HRCT scan will be obtained by the investigator or a person designated by the investigator (if acceptable by the local regulations).

For consenting patients whose eligibility assessment was determined using a historical standard-of-care scan, a study specific baseline HRCT scan will be required prior to randomization. Consenting patients will have a follow-up pulmonary HRCT scan performed at Week 52 to evaluate for qualitative and quantitative changes related to IPF progression. The HRCT films will be centrally reviewed and scored on the basis of texture based analysis for changes in lung fibrosis on the basis of quantitative computer tomography. Changes in quantitative computer tomography scores will be calculated as an exploratory endpoint and assessed relative to disease progression, spirometry parameters, and other efficacy measures.

4.5.9 Surgical Lung Biopsy

Surgical lung biopsies are not required for eligibility into the study. Patients who have undergone a surgical lung biopsy should have slides sent for SLB central review assessment to confirm eligibility in accordance with the 2011 ATS/ERS/JRS/ALAT consensus statement. The central review pathologist will evaluate submitted slides for UIP Pattern (UIP, Probable UIP, Possible UIP, Non-classifiable, or Inconsistent with UIP). The histopathologic assessment criteria are outlined in [Appendix 11](#).

Those with an HRCT central review assessment of “UIP” will not be required to submit SLB slides for central review if documentation of a “UIP” or “Probable UIP” pattern can be provided by a pathologist qualified in reviewing IPF biopsies.

Assessments from the SLB central review will be entered into the eCRF, and results will be provided to sites for eligibility determination.

4.5.10 Pirfenidone Background Therapy (Cohort B)

IPF background therapy in Cohort B is pirfenidone. Pirfenidone licensed as ESBRIET or PIRESPA may be locally sourced for patients with access through their healthcare provider until it is provided by the Sponsor as IMP through the IxRS system. Patients consenting for Cohort B who are currently on a stable dose of pirfenidone (licensed as ESBRIET or PIRESPA) ≤ 2403 mg/d for ≥ 4 weeks will start the standard screening period of 28 days (± 14 days). Those patients who meet all eligibility criteria will then be randomized 1:1 to double blind treatment with SC lebrikizumab 250 mg or placebo every 4 weeks. Patients consenting to Cohort B who are not treated with pirfenidone at the time of screening will complete all screening assessments prior to initiating the pirfenidone titration run-in period. The Sponsor will provide background pirfenidone IMP to all patients who meet eligibility criteria within the 28-day (± 14 days) screening window. Pirfenidone titration and optimal patient dose will be determined during the 4–6 weeks “run-in” period to establish pirfenidone tolerability. A minimum period of 4 weeks from the first dose of pirfenidone will be required prior to randomization. Dose titration will

proceed based upon pirfenidone label guidance (see Section 4.3.4). If a patient experiences significant side effects, treatment of symptoms and/or temporary dose modifications should be considered (Costabel et al. 2014). The decision to modify pirfenidone dosing is ultimately the responsibility of the investigator; however, occasional day-to-day variability in dosing due to patient initiative and preference is expected to occur. Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.4. For patients treated with PIRESPA (limited to Japan), dose titration and management of adverse effects should be based upon guidance in the marketed product label, including a maximum recommended dose ≤ 1800 mg/d. Patients who fail to tolerate pirfenidone will be run-in failed and will not be randomized to this study.

4.5.11 Non-Elective Hospitalizations

At each study visit, the investigator will ask directed questions to assess the possibility that the patient experienced a non-elective hospitalization(s) per protocol over the preceding 4 weeks. Given that non-elective hospitalizations are a component of the primary endpoint in this study, a dedicated eCRF will be used to record information regarding a protocol-defined hospitalization event. A hospitalization must also be reported as a serious adverse event as per Section 5.2.2.

4.5.12 Protocol-Defined Idiopathic Pulmonary Fibrosis Exacerbation

At each study visit, the investigator will ask directed questions and review the file to assess the possibility that the patient experienced an acute IPF exacerbation per protocol over the preceding 4 weeks. A dedicated eCRF will be used to record information regarding a protocol defined acute IPF exacerbation. An acute IPF exacerbation should also be reported as an adverse event (or serious adverse event as applicable) as per Section 5.2 and Section 5.3.5.9. A *protocol-defined* acute IPF exacerbation is defined as an event that meets **all** of the following criteria as determined by the investigator:

- Unexplained worsening or development of dyspnea within the previous 30 days
- Radiologic evidence of new bilateral ground-glass abnormality or consolidation, superimposed on a reticular or honeycomb background pattern that is consistent with UIP
- Absence of alternative causes, such as left heart failure, pulmonary embolism, pulmonary infection (on the basis of endotracheal aspirate or bronchoalveolar lavage if available, or investigator judgment), or other events leading to acute lung injury (e.g., sepsis, aspiration, trauma, reperfusion pulmonary edema)

4.5.13 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 Six-Minute Walk Test (ATS Statement 2002).

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

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 or < 60 beats per minute
- Systolic blood pressure > 180 mmHg
- Diastolic blood pressure > 100 mmHg

Prior to performing any study-related 6MWTs, patients will undergo an oxygen titration protocol to determine the necessary O₂ flow rate (if any) for the screening 6MWT. The flow rate identified during the oxygen titration procedure will also be the stable flow rate that the patient remains on for all subsequent 6MWTs for the entire study duration. The titration procedure will be standardized as follows:

1. The patient should be seated for at least 10 minutes while breathing room air.
2. A room air SpO₂ will be obtained.
3. If the patient's SpO₂ is ≥ 88% the oxygen titration protocol can be stopped. All 6MWTs in this case should be performed on room air (0 L/min).
4. If the patient's SpO₂ is < 88%, he or she should be started on O₂ at the rate of 2 L/min and allowed to rest for 5 minutes.
5. If the patient's SpO₂ is ≥ 88% on 2 L/min after 5 minutes, the oxygen titration protocol can be stopped. All 6MWTs in this case should be performed on 2 L/min.
6. If the patient's SpO₂ is < 88% after 5 minutes, Steps 4 and 5 should be repeated on 4 L/min and 6 L/min (if necessary).
7. The maximum allowed O₂ flow rate for study-related 6MWTs is 6L/min. Patients whose SpO₂ is not ≥ 88% on 6 L/min after 5 minutes will be excluded from all 6MWTs.

Screening and all subsequent 6MWT procedures will occur with the patient receiving the O₂ 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. SpO₂ should be measured before all study-related 6MWTs after the patient has been at rest for 5 minutes while receiving their titrated O₂ requirement. Any patient who has an SpO₂ of < 85% after 5 minutes should not undergo the procedure during that visit.

SpO₂ should not be monitored during the 6MWT procedure. Patients should undergo the procedure without any encouragement and may temporarily or permanently stop walking at their discretion. 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

Oxygen flow rate will be recorded before every 6MWT. Heart rate, SpO₂, and the Borg CR10 Scale will be recorded immediately before and after the procedure.

4.5.14 Laboratory Assessments

Laboratory samples will be obtained according to the schedules in [Appendix 1](#), [Appendix 2](#), [Appendix 3](#), and [Appendix 4](#). Clinically significant abnormal laboratory findings discovered during the screening period should be recorded on the Medical History and Baseline Conditions eCRF as a diagnosis, rather than recording actual laboratory values. On days of study drug administration, predose laboratory samples should be drawn 0-4 hours before the injection, unless otherwise specified.

Samples for the following standard laboratory tests will be sent to the study sites' local laboratory for analysis:

- Urine pregnancy test

All women of childbearing potential (including those who have had a tubal ligation) will have urine pregnancy tests performed prior to dosing and at other specified visits (see [Appendix 1](#), [Appendix 2](#), [Appendix 3](#), and [Appendix 4](#)). If a urine pregnancy test result is positive, study treatment will not be administered that day, and the result must be confirmed by a serum pregnancy test (conducted at a central laboratory; see below). Women with a confirmed pregnancy must discontinue study treatment.

- Serum tryptase (obtained 1–6 hours after the acute onset of symptoms of an anaphylactic, anaphylactoid, or serious hypersensitivity reaction), whenever possible

Samples for the following standard laboratory tests will be sent to a central laboratory for analysis or for storage until shipped to a reference laboratory for testing:

- Hematology: RBC count, WBC count, hemoglobin, hematocrit, platelet count, and WBC differential count (neutrophils, bands, lymphocytes, eosinophils, basophils, monocytes, and other cells). The Principal Investigator, all clinical study site staff and Sponsor study management team will be blinded to values of blood eosinophil and monocytes for randomized patients to prevent unintentional unblinding of the study. These values will be monitored by an external Medical Monitor identified by the Sponsor to ensure patient safety is monitored.
- Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase, creatinine phosphokinase, and uric acid
- B-type Natriuretic protein
- Serum pregnancy test
 - All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test performed at screening and to confirm any subsequent positive urine pregnancy test result. Women with a confirmed pregnancy will be excluded from study participation and must discontinue study treatment. Refer to Section 5.4.3.1 for management of a patient with a confirmed pregnancy.
- Urinalysis: protein, blood, glucose, and microscopic examination (RBCs, WBCs, casts, and crystals)

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

- Serum samples for antibodies and anti-PLB2 *antibody* testing
- Serum samples for PK assessments (free lebrikizumab concentrations)
- Serum and plasma samples for exploratory research on IL-13– or IPF-related biomarkers (e.g., periostin, CCL18, YKL40, COMP, OPN, CCL13)

For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual.

4.5.14.1 Electrocardiograms

Single digital 12-lead ECG recordings will be obtained at screening, Week 24, and Week 52 of the placebo-controlled periods for Cohort A and Cohort B, and at Week 104/52OL for open-label lebrikizumab treatment in Cohort A, and at the last scheduled Safety Follow-Up Visit 14 weeks after EOT. Standard local procedures for obtaining high-quality ECGs should be followed.

ECGs for each patient will be collected on standardized equipment provided by the Sponsor. To minimize variability, it is important that patients be in a resting position

for ≥ 5 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 meals and any scheduled study procedures (e.g., vital sign measurements, blood draws, and study drug administration if applicable). ECGs should be performed at least 4 hours after the last short-acting beta-agonist dose and at least 12 hours after the last LABA dose.

ECG data will be captured, annotated, and centrally read by a single, blinded, independent cardiologist at a central ECG laboratory.

The investigator or designee must review, sign, and date all ECG tracings. For safety monitoring purposes, any abnormalities on any of the ECGs will be documented in the ECG file by the investigator. Any ECG changes that are associated with symptoms or lead to a change in study treatment or concomitant treatment or discontinuation from study treatment must be reported as an adverse event on the adverse event eCRF (see Section 5.2). Paper copies of the ECGs will be kept as part of the patient's permanent study file at the site.

4.5.15 Patient-Reported Outcomes

Patient-reported outcome (PRO) data will be elicited from the patients in this study to more fully characterize the clinical profile of lebrikizumab. The PRO questionnaires, translated as required in the local language, will be completed in their entirety by the patient at specified timepoints during the study (see [Appendix 1](#), [Appendix 2](#), [Appendix 3](#), and [Appendix 4](#)). The ATAQ-IPF, SGRQ, and EQ-5D should be self-administered at the investigational site prior to all other non-PRO assessments and before the patient receives any disease-status information or study drug during that assessment. The Borg CR10 Scale should be administered immediately before and after the 6MWT prior to all other non-PRO assessments and before the patient receives any disease-status information or study treatment during that assessment. However, spirometry and DL_{CO} may be performed during Visit 1 before 6MWT at the discretion of the investigator. In all cases, each study assessment should be done in the same order at subsequent visits.

4.5.15.1 A Tool to Assess Quality of Life in Idiopathic Pulmonary Fibrosis

The ATAQ-IPF is an IPF-specific quality-of-life questionnaire. The original version of the ATAQ-IPF contains 74 items ([Swigris et al. 2010](#)). Version 3 will be implemented in this study. Version 3 of the ATAQ-IPF includes 31 items within five domains: cough (6 items), dyspnea (7 items), exhaustion (6 items), emotional well-being (6 items), and independence (6 items). Each item of the ATAQ-IPF is assessed on a scale ranging from 1 (Strongly disagree) to 4 (Strongly agree). The ATAQ-IPF has a recall specification of 2 weeks. A copy of the questionnaire is provided in [Appendix 5](#).

4.5.15.2 St. George's Respiratory Questionnaire

The SGRQ is a 50-item health-related quality-of-life instrument that measures health impairment (Jones et al. 1992). The SGRQ was originally developed for use in COPD and asthma populations; however, it has been used to assess health impairment in IPF populations. The questionnaire contains three domains: symptoms, activity, and impacts. Items are assessed on various response scales, including a 5-point Likert scale and True/False scale. The SGRQ has a recall specification of 4 weeks. A copy of the questionnaire is provided in [Appendix 6](#).

4.5.15.3 EuroQol 5-Dimension Questionnaire

The EQ-5D is a generic preference-based health-related quality of life questionnaire that provides a single index value for health status (Rabin and de Charro 2001). This tool includes questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression that are used to build a composite of the patient's health status. The EQ-5D questionnaire will be utilized in this study for economic modeling. A copy of the questionnaire is provided in [Appendix 7](#).

4.5.15.4 Borg Category Ratio 10 Scale®

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). In this study, the instrument will be used to assess dyspnea from the patient's perspective. The Borg CR10 Scale ranges from 0 (Nothing at all) to 10 • (Absolute maximum/Highest possible). A copy of the assessment is provided in [Appendix 12](#).

4.5.16 Optional Samples for Roche Clinical Repository

4.5.16.1 Overview of the Roche Clinical Repository

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- [REDACTED]

4.5.16.2 Approval by the Institutional Review Board or Ethics Committee

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

4.5.16.3 Sample Collection

The following samples will be collected for identification of dynamic (non-inherited) biomarkers:

- Residual PD and PK serum samples for research purposes, including but not limited to research on biomarkers related to IL-13, IPF, IPF-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, IPF, IPF-related diseases, or other respiratory diseases

The following samples will be collected for identification of genetic (inherited) biomarkers:

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

The purpose of collecting optional RNA samples is to increase the understanding of peripheral blood gene expression in patients with IPF with and without lebrikizumab. 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 used or that will be used for treatment of IPF, as well as to understand the relationship between heritable factors and clinical features of IPF. These studies might also help to increase understanding of the disease.

For all samples, dates of consent and specimen collection should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics 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/IEC-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.

4.5.16.4 Confidentiality

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4.5.16.5 Consent to Participate in the Roche Clinical Repository

The ICF 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 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.

4.5.16.6 Withdrawal from the Roche Clinical Repository

[REDACTED]

4.5.16.7 Monitoring and Oversight

RCR specimens will be tracked in a manner consistent with Good Clinical Practice 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 ICF. 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/IEC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

4.5.17 Timing of Study Assessments

4.5.17.1 Screening and Pretreatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. ICF completion must occur before any other Visit 1 procedures are initiated.

ICFs for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Screening tests and evaluations will be performed within 28 ± 14 days prior to randomization (Day 1, Visit 2) or the start of run-in (Visit 1.5), where required, unless otherwise specified. For Cohort B, all screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before the pirfenidone titration run-in period (Visit 1.5) and/or randomization Visit 2 are scheduled. A minimum period of 4 weeks may be required to establish pirfenidone tolerability prior to the randomization

visit (Day 1, Visit 2) for patients in Cohort B. 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.

A serum sample to assess periostin must be collected and shipped to the central laboratory during the first 2 weeks of screening.

Re-screening refers to repeating the entire screening process, with the exception of HRCT/SLB results. Re-screening is required if a patient has not met all of the eligibility criteria within the screening period. Patients are allowed to be re-screened for selected reasons up to two times. Each patient must be re-consented before re-screening occurs. See [Appendix 1](#) and [Appendix 3](#) for the schedule of screening and pretreatment assessments.

4.5.17.2 Assessments during Treatment

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](#), [Appendix 2](#), and [Appendix 3](#)). Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the schedule of assessments. The ATAQ-IPF, SGRQ, and EQ-5D should be self-administered at the investigational site prior to all other non-PRO assessments and before the patient receives any disease-status information or study drug during that assessment. The Borg CR10 Scale should be administered immediately before and after the 6MWT prior to all other non-PRO assessments and before the patient receives any disease-status information or study treatment during that assessment. However, spirometry and DL_{CO} may be performed during Visit 1 before 6MWT at the discretion of the investigator. In all cases, each study assessment should be done in the same order at subsequent visits. See [Appendix 1](#), [Appendix 2](#), and [Appendix 3](#) for the schedules of assessments performed during the minimum and maximum treatment periods.

4.5.17.3 Assessments at Study Completion/Early Termination Visit

The study completion visit occurs as part of the last Safety Follow-up Visit (see [Appendix 1](#), [Appendix 2](#), and [Appendix 3](#)). All patients will be monitored for safety for 18 weeks after receipt of the final dose of lebrikizumab or placebo study treatment.

Patients who choose to prematurely discontinue study drug will be encouraged to remain in the study and complete all remaining assessments. If this is not feasible, the patient should enter and complete the safety follow-up period unless consent has been withdrawn.

Patients who withdraw from the study (regardless of the reason) and refuse safety follow-up will be asked to return to the clinic within 30 days (± 7 days) after the last dose of study treatment for an early termination visit. Refer to [Appendix 1](#), [Appendix 2](#), and

[Appendix 3](#) for the schedules of assessments performed at the study completion or early termination visit.

4.5.17.4 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. Refer to [Appendix 4](#) for the schedule of assessments performed at the follow-up visit.

4.5.17.5 Assessments at Unscheduled Visits

See [Appendix 1](#), [Appendix 2](#), [Appendix 3](#), and [Appendix 4](#) for assessments that are required in case of an unplanned visit. An unscheduled visit may occur at any time during the study.

4.6 PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

The investigator has the right to discontinue a patient from study drug or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason. Reasons for discontinuation of study drug or 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
- Patient noncompliance, such as missing scheduled visits, non-adherence with medications, etc.

4.6.1.1 Discontinuation from Study Drug

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

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

Patients who discontinue study treatment should continue to complete all scheduled study assessments and if unable or unwilling to complete these assessments should at minimum enter the safety follow-up period. All patients should be followed for safety for 18 weeks after the last dose of lebrikizumab or placebo study treatment. The primary reason for premature study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

4.6.1.2 Withdrawal from Study

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. 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 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 replace a site at any time. Reasons for replacing 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) guidelines for Good Clinical Practice

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

5.1.1 Adverse Events of Special Interest for Lebrikizumab

Based on data to date, the theoretical risks associated with IL-13 inhibition, and the risks associated with and for biologic agents in general, *the following* four categories of potential adverse events have been identified as adverse events of special interest for lebrikizumab (refer to the Lebrikizumab IB for more details):

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

Collection of information about these events allows for better evaluation and understanding of any potential safety risk to patients (refer to the Lebrikizumab IB for more details).

The documentation and expedited reporting requirements for these adverse events of special interest are described in Section 5.2.2 (reporting of serious events) and Section 5.2.3 (reporting of events of special interest).

The following risk mitigation measures apply to patients receiving the study drug. Adherence to the planned dose regimen of study drug is required unless dosing is held for safety reasons. For study visits at which the study drug dose is withheld because of toxicity, all other study assessments should be performed as per the study schedule.

Recommendations for vigilance with regard to signs and symptoms of particular safety events of interest are summarized in the following sections.

5.1.1.1 Local Injection-Site Reactions

In *recently*-completed Phase III clinical trials with lebrikizumab administered to patients with asthma, *the reported rate of injection-site reactions was comparable between the group of patients who were treated with lebrikizumab and the group of patients who were treated with placebo (117 of 1432 patients [8.2%] vs. 55 of 716 patients [7.7%], respectively). In Cohort A of Study GB28547 (RIFF), injection site reactions were reported in 13 of 78 patients (16.7%) who were treated with lebrikizumab compared with 6 of 76 patients (7.9%) who were treated with placebo. These events were all non-serious and in most cases did not require treatment.*

A local injection-site reaction is any local reaction occurring at the site of injection following study drug administration. Local injection-site reactions including but not limited to erythema, induration, and pain, should be reported immediately to the Sponsor as adverse events of special interest and as serious adverse events if appropriate. The event term should be recorded in the Adverse Event eCRF as the symptom preceded by 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 treatment(s) should be reported on the eCRF. Injection-site reactions will be monitored closely, with site training in the recognition and reporting of events immediately to the Sponsor as adverse events of special interest and as serious adverse events if appropriate. Detailed information regarding injection-site reactions 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).

5.1.1.2 Anaphylactic, Anaphylactoid, and Hypersensitivity Reactions

Anaphylactic, anaphylactoid, and hypersensitivity reactions *to treatment* are considered a potential risk with all biologic medications, including lebrikizumab. *On the basis of newly-available safety data from six studies that were recently unblinded to the study treatment, there were no reports of anaphylaxis per the Sampson's criteria assessed as related to lebrikizumab treatment by an independent external adjudication committee that was blinded to the study treatment. Furthermore, in the study of patients with IPF (Study GB28547, Cohort A) and both atopic dermatitis studies (Study GS29250*

and Study GS29735), there were no reported events of anaphylaxis, anaphylactoid, or serious hypersensitivity reactions meeting search criteria.

Patients with a history of a severe allergic 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., cramping, abdominal pain, vomiting)

Investigators and health care professionals administering lebrikizumab will receive guidance on how 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 8](#)). Investigators and health care professionals should also be trained to accurately and appropriately report these events immediately to the Sponsor as adverse events of special interest or as serious adverse events if appropriate (see [Section 5.2](#)).

Health care professionals should also instruct patients on how to recognize the signs and symptoms of any anaphylactic, anaphylactoid, or hypersensitivity reaction and contact a health care provider or seek emergency care in case of any such symptoms. Patients will need to be clinically stable prior to each dose of study drug as assessed by clinical evaluations including vital signs and resting pulse oximetry.

Patient injections will be administered by a qualified health care professional *or a trained non-health care professional who can legally administer injections*. Patients will be monitored *by a qualified health care professional* for a minimum of 1 hour after dosing for the first three treatment visits and for 30 minutes after dosing for all *subsequent* treatment visits.

If a patient experiences a suspected non-serious hypersensitivity reaction, the case should be discussed with the Medical Monitor prior to continued dosing. If a patient has signs or symptoms of an anaphylactic, anaphylactoid, or serious hypersensitivity reaction, administration of the study drug must be discontinued permanently (refer to [Appendix 8](#) 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 4.6.1.1](#)). A blood sample for measuring total tryptase level should be obtained 1–6 hours after the acute onset of symptoms, whenever possible. The tryptase sample will be collected and

analyzed per the site's local laboratory practice. Blood samples for antibody testing and PK analysis should be obtained at the time of the event whenever possible, and a blood sample for antibody testing should be obtained at the first follow-up visit after the event (e.g., Safety Follow-Up Visit 1; see [Appendix 4](#)).

Detailed information regarding anaphylactic, anaphylactoid, or hypersensitivity reactions 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](#)).

5.1.1.3 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 attention for possible symptoms of *L. monocytogenes* infection. Patients with an active parasitic infection or *L. monocytogenes* infection within 6 months prior to Day 1 will be excluded from study participation.

The role of IL-13 in other infections is less clear. *Safety analysis data from five studies (with the exclusion of Study GB28547) that were recently unblinded to the study treatment show that lebrikizumab treatment is not associated with infections and overall, there were no imbalances in infections (both broad and narrow [MedDRA High-Level Group Term of helminthic disorders, mycobacterial infectious disorders, and protozoal infectious disorders, or MedDRA High-Level Term of listeria infections]). Analysis results from Cohort A of Study GB28547 showed higher rates of infection (broad) in the group of patients who were treated with lebrikizumab versus those who were treated with placebo (51 of 78 patients [65.4%] vs. 41 of 76 patients [53.9%], respectively), which was driven mainly by an imbalance in urinary tract infections (UTIs) between the groups of patients. All patients who were treated with lebrikizumab and showed a UTI had predisposing risk factors, including a single serious adverse event of UTI that occurred in a patient with prostatic hyperplasia.*

In Phase III studies of patients with moderate-to-severe asthma, herpes infections including herpes zoster (shingles) were reported in 2.0% of patients who were treated with lebrikizumab compared with 0.7% of patients who were treated with placebo. In a Phase II study of patients with moderate-to-severe atopic dermatitis, herpes infections including herpes zoster (shingles) were reported in 3.8% of the patients who were treated with lebrikizumab. None of the herpes infections that were reported, including herpes zoster, required a hospital admission. In Cohort A of Study GB28547, herpes viral infections in patients were reported but there were no imbalances noted between

patients who were treated with lebrikizumab and patients who were treated with placebo. Refer to the Lebrikizumab IB for more detail.

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 will be excluded from study participation if they experience an episode of infection requiring hospitalization for ≥ 24 hours or treatment with antibiotics (IV, oral, or inhaled) within 4 weeks prior to Day 1 or during screening.

Patients with an active upper or lower respiratory tract infection occurring at any time within the screening period prior to the randomization visit (Visit 1 to Day 1, Visit 2) 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, should be reported immediately to the Sponsor as adverse events of special interest and as serious adverse events, if appropriate. Detailed information with regard to 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.

5.1.1.4 Malignancies

The impact of IL-13 inhibition on the development of malignancies is not known; however, malignancies have been identified as a potential concern for other biologic agents. In the completed Phase II asthma studies, 1 patient experienced malignant melanoma in situ and a basal cell carcinoma approximately 10 weeks after the initiation of treatment with lebrikizumab. Both events were considered by the investigator to be unrelated to lebrikizumab.

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 during the study (including basal or squamous cell carcinoma of the skin or carcinoma in situ).

Malignancies should be reported immediately to the Sponsor as adverse events of special interest 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).

[REDACTED]

5.1.3 Other Area of Interest: Immunogenicity

As with administration of any exogenous protein, a potential exists for the development of ATAs to lebrikizumab, which could have neutralizing or sensitizing effects resulting in reduced efficacy or safety. Data obtained to date in completed clinical trials do not suggest increased incidence of ATAs with lebrikizumab treatment. In the few patients with positive post-treatment ATA assessments in completed trials, no clinically detectable response as assessed by PK, efficacy, or safety data was seen. A positive antibody response to PLB2 has been observed in asthma 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. Refer to the Lebrikizumab IB for more detail.

To assess for the development of immunogenicity, antibody samples will be obtained at baseline, at regular intervals during treatment, and during the safety follow-up period (see [Appendix 1](#), [Appendix 2](#), [Appendix 3](#), and [Appendix 4](#)). Antibody response to lebrikizumab and PLB2 will be assessed.

To ensure that an accurate assessment of immunogenicity is obtained, a final antibody sample will be obtained from all patients at the final visit, whether that occurs at study completion or early discontinuation. With the exception of patients who withdraw from the study early, this sample will typically be obtained following completion of a 14-week follow-up period, which will allow the drug to clear for ≥ 5 half-lives.

Samples will be stored appropriately for further evaluation as needed.

5.1.4 Adverse Events of Special Interest for Pirfenidone

Summary data from Phase III studies indicate that pirfenidone is generally well tolerated. The most common adverse events were gastrointestinal disorders and skin disorders, which are typically mild to moderate and can be managed by dose modification. Mild or

moderate serum transaminase elevations (serum ALT or AST > 3 × ULN) occurred more frequently in patients who were treated with pirfenidone 2403 mg/d than in patients who were treated with placebo, but they were most often effectively managed with dose modification.

It is the responsibility of the investigator to monitor patients for toxicities as frequently as clinically indicated and consistent with the instructions of the package inserts for any medication used to treat a study patient. Refer to Section 6.1 on the safety data established in Phase III studies.

If a patient experiences significant side effects, treatment of symptoms and/or temporary dose reductions, interruptions, or discontinuation of pirfenidone treatment should be considered. Any such dosing modifications should be recorded in the patient eCRF. Contact the Roche Medical Monitor or designee to discuss the management of adverse events and dose modification, as needed.

5.1.4.1 Elevated Liver Enzymes

Increases in ALT and AST > 3 × ULN have been reported in patients treated with pirfenidone. Rarely these have been associated with concomitant elevations in bilirubin. Patients treated with pirfenidone 2403 mg/day in the three Phase 3 trials had a higher incidence of elevations in ALT or AST ≥ 3 × ULN than placebo patients (3.7% vs. 0.8%, respectively). Elevations ≥ 10 × ULN in ALT or AST occurred in 0.3% of patients in the pirfenidone 2403 mg/day group and in 0.2% of patients in the placebo group. Increases in ALT and AST ≥ 3 × ULN were reversible with dose modification or treatment discontinuation. No cases of liver transplant or death due to liver failure that were related to pirfenidone have been reported. However, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that could lead to death or the need for liver transplants in some patients.

Conduct liver function tests (ALT, AST, and bilirubin) prior to the initiation of therapy with pirfenidone in all patients, then monthly for the first 6 months and every 3 months thereafter, per ESBRIET package insert instructions. Dosage modifications or interruption may be necessary for liver enzyme elevations. These guidelines must be followed for any patient who may initiate pirfenidone treatment, whether as rescue therapy in Cohort A or background therapy in Cohort B.

Dosage Modification due to Elevated Liver Enzymes

Dosage modifications or interruptions may also be necessary when liver enzyme and bilirubin elevations are exhibited. For liver enzyme elevations, modify the dosage as follows:

If a patient exhibits >3 but $\leq 5 \times$ ULN ALT and/or AST without symptoms or hyperbilirubinemia after starting ESBRIET therapy:

- Discontinue confounding medications, exclude other causes, and monitor the patient closely.
- Repeat liver chemistry tests as clinically indicated.
- The full daily dosage may be maintained, if clinically appropriate, or reduced or interrupted (e.g., until liver chemistry tests are within normal limits) with subsequent re-titration to the full dosage as tolerated.

If a patient exhibits >3 but $\leq 5 \times$ ULN ALT and/or AST accompanied by symptoms or hyperbilirubinemia:

- Permanently discontinue ESBRIET.
- Do not rechallenge patient with ESBRIET.

If a patient exhibits $>5 \times$ ULN ALT and/or AST:

- Permanently discontinue ESBRIET.
- Do not rechallenge patient with ESBRIET.

5.1.4.2 Photosensitivity Reaction or Rash

Patients treated with ESBRIET 2403 mg/day in the three Phase 3 studies had a higher incidence of photosensitivity reactions (9%) compared with patients treated with placebo (1%). The majority of the photosensitivity reactions occurred during the initial 6 months. Instruct patients to avoid or minimize exposure to sunlight (including sunlamps), to use a sunblock (SPF 50 or higher), and to wear clothing that protects against sun exposure. Additionally, instruct patients to avoid concomitant medications known to cause photosensitivity. Dosage reduction or discontinuation may be necessary in some cases of photosensitivity reaction or rash.

5.1.4.3 Gastrointestinal Disorders

In the clinical studies, gastrointestinal events of nausea, diarrhea, dyspepsia, vomiting, gastro-esophageal reflux disease, and abdominal pain were more frequently reported by patients in the ESBRIET treatment groups than in those taking placebo. Dosage reduction or interruption for gastrointestinal events was required in 18.5% of patients in the 2403 mg/day group, as compared to 5.8% of patients in the placebo group; 2.2% of patients in the ESBRIET 2403 mg/day group discontinued treatment due to a gastrointestinal event, as compared to 1.0% in the placebo group. The most common ($>2\%$) gastrointestinal events that led to dosage reduction or interruption were nausea, diarrhea, vomiting, and dyspepsia. The incidence of gastrointestinal events was highest

early in the course of treatment (with highest incidence occurring during the initial 3 months) and decreased over time. Dosage modifications may be necessary in some cases of gastrointestinal adverse reactions.

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, measurement of protocol-specified safety laboratory assessments, measurement of protocol-specified vital signs, and 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 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 5.3.5.9
- 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 procedures such as spirometry or 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:

- Fatal (i.e., the adverse event actually causes or leads to death)
- 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 5.3.5.10)
- 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)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- 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 (rated as mild, moderate, or severe; 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)

Adverse events of special interest 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). Adverse events of special interest for this study include the following:

- Adverse events of special interest for general drug development
 - Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Section 5.3.5.6
 - Suspected transmission of an infectious agent by the study drug, as defined below:
 - 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 indicating 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 lebrizumab (see Section 5.1.1 for further information)
 - Local injection-site reactions
 - Anaphylaxis, anaphylactoid and hypersensitivity reactions
 - Infections

Malignancies

- *Adverse events of special interest for pirfenidone*

Elevated liver enzymes (to report cases of elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Section 5.3.5.6)

Photosensitivity reaction or rash

Gastrointestinal disorders

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 Sections 5.4, 5.5, and 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**, serious adverse events caused only by a protocol-mandated intervention should be reported (e.g., serious adverse events related to procedures such as biopsies or spirometry) or protocol mandated washout of medications. See Section 5.4.2 for reporting requirements of Serious Adverse Events.

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until study completion. After this period, the investigator does not need to actively monitor patients for adverse events. Once the study has ended the Sponsor should be notified if the investigator becomes aware of any serious adverse events and adverse events of special interest (see Section 5.6).

For Cohort B only: Safety findings should be reported for patients who are administered background pirfenidone by their health care provider. Safety findings should be collected as of date of consent for the study for patients who are naive to pirfenidone treatment. Safety findings should be collected on the dates when pirfenidone is taken (see Section 4.5.10).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted to elicit 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 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 (where 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 (e.g., accident, new or intercurrent disease)

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

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 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 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.

5.3.5.2 Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring 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. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events 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 subsequent 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.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously without resolution between patient evaluation timepoints. Such events should be recorded only once on the Adverse Event eCRF. Initial adverse event intensity should be recorded at the time the adverse event is reported. If a persistent adverse event becomes more severe, the most extreme intensity should also be recorded in the Adverse Event eCRF. For example, a headache Grade 1 increases to headache Grade 2. At the time of the intensity change, the Grade 2 intensity should be recorded in the Adverse Event eCRF in the most extreme intensity data field.

If at any time the non-serious adverse event qualifies as a serious adverse event per the seriousness criteria (refer to Section 5.3.3), the Adverse Event eCRF should be updated to reflect this and 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). To update the Adverse Event eCRF, change the seriousness criteria to “serious” from “non-serious,” provide the date the event became serious, and complete all subsequent data fields on the Adverse Event eCRF.

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

5.3.5.4 Abnormal Laboratory Values

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

- 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
- 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 five times the upper limit of normal [ULN] associated with cholecystitis), only the diagnosis (i.e., cholecystitis) 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 whether 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or

seriousness should be updated any time the event worsens (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.5 Abnormal Vital Sign Values

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

- 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
- 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

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

- Treatment-emergent ALT or AST $>3 \times \text{ULN}$ in combination with total bilirubin $>2 \times \text{ULN}$
- Treatment-emergent ALT or AST $>3 \times \text{ULN}$ 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 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 5.4.2).

5.3.5.7 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 IPF.

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 of 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 IPF, “IPF progression” should be recorded on the Adverse Event eCRF.

5.3.5.8 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”).

5.3.5.9 Lack of Efficacy or Worsening of Idiopathic Pulmonary Fibrosis

Medical occurrences or symptoms of deterioration that are anticipated as part of IPF 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 IPF on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., “worsening of IPF” or “IPF progression”).

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization 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 serious adverse events:

- Hospitalization for respite care
- Planned hospitalization required by the protocol
- 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 suffered an adverse event

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

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose studied. An overdose, incorrect administration of study drug, or incorrect kit administration is not an adverse event unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

All adverse events associated with an overdose, incorrect administration, or incorrect kit administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills a seriousness criterium, 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).

5.3.5.12 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data. However, if any patient responses suggestive of a possible adverse event are identified during site review of the PRO questionnaires, the site staff will alert the investigator, who will determine whether 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/IEC.

5.4.1 Emergency Medical Contacts: Operations/Clinical

Medical Monitor (Roche Medical Responsible) Contact Information is as follows:

Primary Contact

Medical Monitor: [REDACTED], M.D.
Telephone No.: [REDACTED]
Mobile Telephone No.: [REDACTED]

Secondary Contact

Medical Monitor: [REDACTED] M.D.
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 and 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 Occurring prior to Initiation of Study Drug

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. A paper Serious Adverse Event/Adverse Event of Special Interest CRF and Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), with use of the fax numbers provided to investigators. Patients who undergo screening procedures but do not enroll in the study will have serious adverse events recorded only in the Roche Drug Safety database and not in the study's clinical database.

5.4.2.2 Events Occurring after Initiation of Study Drug

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until study completion. 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.

For Cohort B only: Safety findings should be reported for patients who are administered background pirfenidone by their health care provider. Safety findings should be collected as of date of consent for the study for patients who are naive to pirfenidone treatment. Safety findings should be collected on the dates when pirfenidone is taken (see Section 4.5.10).

In the event that the EDC system is unavailable, a paper clinical trial Serious Adverse Event/Adverse Event of Special Interest reporting form and Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), with use of the fax numbers or email 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 lebrikizumab or placebo 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, a Clinical Trial Pregnancy Reporting form and Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), with use of the fax numbers or email 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 always be classified as serious (because the Sponsor considers these 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 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

The investigator must report all medical device complaints related to the prefilled syringe or other medical device used in the study 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 within 1 working day (refer to the pharmacy manual for further details). If any medical device complaint results in an adverse event, to the study patient the adverse 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 and submitted through the EDC immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.4.2. If the medical device complaint results in an adverse event to an individual other than the study patient, the device complaint must be reported on the IMP Deviation Form and the adverse event must be reported as a spontaneous adverse event to Roche Safety Risk Management via telephone.

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 study-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. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

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, reporting instructions provided in Section 5.4.3.1 should be followed.

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, or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, or autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

Following the Adverse Event Reporting Period (see Section 5.3.1), the investigator does not need to actively monitor patients for 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, if the event is believed to be related to prior study drug treatment.

The investigator should report the event directly to Roche Safety Risk Management via telephone or via facsimile using the Serious Adverse Event/Adverse Event of Special Interest Reporting Form.

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, IECs, 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 documents:

- Lebrikizumab IB
- Pirfenidone Core Safety Information (approved labels)

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 analysis of data from the placebo-controlled period *for each cohort* will be performed when all patients have either completed the *end of the placebo-controlled treatment (Week 52/EOT)* visit or discontinued early from the study. Treatment assignment will be unblinded to the personnel performing the analysis when all data through the EOT visit are in the database and the data have been cleaned and verified *for each cohort*.

The analysis of complete data for the study, including data from the placebo-controlled period, open-label extension period for Cohort A, and the 14-week safety follow-up period, will be performed when all patients have either completed the placebo-controlled period, open-label extension period for Cohort A, and 14-week safety follow-up period or discontinued early from the study, all data from the study are in the database, and the database is locked. *An interim futility analysis of Cohort B was conducted (see Section 6.8).*

Aggregate results of the placebo-controlled period analysis, summarized by treatment arm, may be reported to the public before completion of the study. However, patients and study site personnel will remain blinded to individual treatment assignment until after the study is completed (after all patients have either completed the placebo-controlled period, open-label extension period for Cohort A, and 14-week safety follow-up period or discontinued early from the study), the database is locked, and the study analyses are final.

Detailed specifications of the statistical methods will be described in the Statistical Analysis Plan (SAP).

6.1 DETERMINATION OF SAMPLE SIZE

In Cohort A, a sample size of 75 patients in each treatment group will provide *approximately 80% power to detect a change in the annualized rate of decline in percentage of predicted FVC over 52 weeks of a 3.7% difference in the means of the absolute change from baseline in percentage of predicted FVC at 52 weeks, assuming*

that the common standard deviation is 8% (as reported in the placebo group in the ASCEND trial of pirfenidone) using a two group t-test with a 0.05 two-sided significance level.

In Cohort B, a sample size of 165 patients in each treatment group will provide *approximately* 80% power to detect a 2.5% difference in the *annualized rate of decline* in percentage of predicted FVC *over* 52 weeks, assuming that the common standard deviation is 8% (as reported in the ASCEND trial of pirfenidone) using a two group t-test with a 0.05 two-sided significance level.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients randomized will be tabulated by study site and treatment arm. Patient disposition (the number of patients randomized, treated, and completing each study period) will be tabulated by treatment arm. Premature treatment discontinuation and study discontinuation as well as reasons for discontinuations will be summarized. Eligibility criteria deviations and other major protocol deviations will be summarized.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics such as age, sex, race/ethnicity, concomitant IPF medication use, comorbid illnesses, and pulmonary function, will be summarized for all randomized patients by treatment arm and perioestin group with use of descriptive statistics. Exposure to study treatment (number of study drug treatments and duration of treatment) will be summarized by treatment arm and study period.

6.4 EFFICACY ANALYSES

The analysis of data from the treatment period in Cohort A will be performed when all patients enrolled in Cohort A have either completed the end of placebo controlled treatment visit (Week 52), or discontinued early from the study. Treatment assignment will be unblinded to the personnel performing the analysis when all data through the Week 52 visit are in the database and the data have been cleaned and verified.

The analysis of data from the treatment period in Cohort B will be performed when all patients enrolled in Cohort B have either completed the end of treatment visit (Week 52) or discontinued early from the study. Treatment assignment will be unblinded to the personnel performing the analysis when all data through the Week 52 visit are in the database and the data have been cleaned and verified.

However, the Sponsor study team directly involved in the study conduct (medical monitoring, clinical operations, drug safety, etc.) will not have access to individual treatment assignments until study completion (*see Section 3.1.3*), when all patients have completed the safety follow-up or discontinued the study. All non-Sponsor personnel who are involved in the conduct of the study (e.g., patients, site monitors, and

investigators) will remain blinded to patient-specific treatment assignments until all patients complete the safety follow-up period or discontinue from the study.

Complete details of the analysis will be provided in the SAP, which will be finalized prior to unblinding the data.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is *annualized rate of decrease in percentage of predicted FVC (% FVC/year) through Week 52.*

The annualized rate of decrease in percentage of predicted FVC will be compared across the treatment arms with the use of a random slope model on observed cases at a 0.05 two-sided significance level.

The statistical model is as follows:

$$FVC_{ijk} = (\beta_0 + \beta_{0k}) + (a_i * \beta_1 + \beta_{1k}) * t_k + \eta_k + \varepsilon_{ijk}$$

where FVC_{ijk} is the predicted FVC for k th patient at visit j in treatment group i ; β_0 is the intercept; a_i and β_1 is the interaction term of the treatment effect ($i = \text{lebrikizumab or placebo}$) and the slope; t_k is the assessment time (continuous in year) for patient k ; η_k is the effect of baseline lung function (defined as $FVC < 50\%$ vs. 50% to 75% vs. $> 75\%$ predicted) for the k th patient; β_{0k} and β_{1k} are the random components for intercept and slope; ε_{ijk} is the random error for k th patient at time j ; β_{0k} , β_{1k} and ε_{ijk} are assumed to be independent and normally distributed with mean 0 and variance of σ_0^2 , σ_1^2 and σ_ε^2 respectively.

Note that because of a relatively large number of strata defined by the randomization stratification factors, the analysis will be adjusted only for baseline lung function because baseline FVC may impact the clinical disease course.

From the model, least squares means for the annualized rate of decline in each treatment arm and the difference between the two treatment arms will be provided with 95% CIs. The model implicitly imputes missing data on the basis of a patient's estimated rate of worsening of lung function prior to the study visit discontinuation (i.e., under the assumption that it is missing at random).

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy end points of this study are as follows:

- PFS, defined as the time from study treatment randomization to the first occurrence of any of the following *disease progression or death events*:

Death from any cause

All-cause hospitalization

A decrease from baseline (*relative change*) of $\geq 10\%$ in FVC (L)

- Annualized rate of *decrease* in FVC (mL/year) over 52 weeks
 - Time from randomization to first *occurrence* of a $\geq 10\%$ absolute decrease in percentage in predicted FVC or death from any cause
 - Annualized rate of *decrease* in percentage of predicted DL_{CO} over 52 weeks
 - Annualized rate of *decrease* in the ATAQ-IPF total score over 52 weeks (see [Appendix 5](#) for a description of the instrument)
 - Time from randomization to non-elective hospitalization or death from any cause
 - Annualized rate of *decrease* in the 6MWT distance over 52 weeks
 - Time from randomization to first event of acute IPF exacerbation (*defined below*)
- IPF exacerbation is defined as an event that meets all of the following criteria as determined by the investigator:

Unexplained worsening or development of dyspnea within the previous 30 days

And radiologic evidence of new bilateral ground-glass abnormality or consolidation, superimposed on a reticular or honeycomb background pattern, that is consistent with UIP

And absence of alternative causes, such as left heart failure, pulmonary embolism, pulmonary infection (on the basis of endotracheal aspirate or bronchoalveolar lavage if available or investigator judgment), or other events that lead to acute lung injury (e.g., sepsis, aspiration, trauma, reperfusion pulmonary edema)

- Time from randomization to first occurrence of SGRQ (see [Appendix 5](#) for a description of the questionnaire) worsening (total score) as defined by reaching MID ([Swigris et al. 2010](#)): Total Score =7 or death from any cause
- Time from randomization to death from any cause

All continuous endpoints will be analyzed with the use of the same methodology as the primary endpoint (see previous section) *with specifics for models and summaries specified in the SAP.*

For time to event endpoints, the log rank test stratified by baseline lung function (FVC <50% vs. 50% to 75% vs. >75% predicted) will be used to compare the time to event endpoints between the two treatment arms. Time will be measured relative to the date of randomization (Day 1). Patients who do not experience the event will have their data censored on the last date during the placebo-controlled period when, on the basis of the assessments in accordance with this protocol, the patient can be considered to have been event-free. Any patients who undergo lung transplantation will be censored at the date of the transplant. Sensitivity analyses will be provided with lung transplant counted as an event for PFS and time from randomization to death or non-elective hospitalization from any cause.

The primary efficacy assessments for the randomized placebo-controlled period are made on the study day of initiation of the open-label lebrikizumab through Week 52. Assessment on this day will be included for analyses of the randomized placebo-controlled period, but subsequent assessment during the open-label period or after Week 52 will be excluded.

The hazard ratio and its 95% CI will be estimated with the use of a Cox regression model stratified by baseline lung function. In fitting the Cox model, ties will be handled with the approximate likelihood method of Efron (1977). Kaplan-Meier curves will be provided.

Summary statistics of the *ATAQ-IPR* and *SGRQ* endpoints and the changes from baseline will be calculated at each assessment time-point for each treatment group. The mean, standard error, and median of the absolute scores and the mean changes from baseline (and 95% CIs) between treatment groups will be reported for the endpoint. For scores involving change from baseline, patients without baseline values will be excluded from the analyses. Line charts depicting the means and mean changes of subscales over time will be also provided. Scoring for the questionnaire will be based on relevant user manuals.

Frequencies and percentages of missing data for the *ATAQ-IPR* and *SGRQ* endpoints will be compared between the two treatment arms.

Additional details for summarization, sensitivity analyses, and type I error control are provided in the SAP.

6.5 SAFETY ANALYSES

Safety analyses will be based on all patients who received at least one dose of *randomized* study drug, with patients grouped according to the actual treatment received. Safety summaries will be presented by treatment arm for all treated patients. *In addition, safety listings will be provided for any events reported during pirfenidone exposure prior to randomization.*

Safety will be assessed through the summary of adverse events, laboratory test results, (including antibodies to lebrikizumab), ECG, and vital signs. These summaries will be produced separately for *each cohort* for the treatment period (placebo-controlled study treatment period, the *Cohort A* open-label lebrikizumab period).

6.5.1 Adverse Events

Verbatim descriptions of treatment-emergent adverse events will be coded and their incidence summarized by treatment arm.

A treatment-emergent adverse event is defined as any new adverse event reported or any worsening of an existing condition reported on or after the first dose of study drug.

In addition, separate summaries will be generated for serious adverse events, deaths, and adverse events leading to discontinuation of study drug.

Analyses will be performed by treatment group for events of special interest that include anaphylactic reactions, local injection-site reactions, infections, and malignancies:

- *Anaphylactic reactions will be reviewed and adjudicated by independent, external experts accordingly to a charter.*
- *Local injection-site reactions will be identified with the use of the MedDRA high-level term of "injection site reaction".*
- *Infections, as identified with the use of the MedDRA system organ class of "infections and infestations"*
- *Malignancies, as identified on the basis of the MedDRA SMQ of "Malignancy" and the subSMQ of "Malignant and unspecified tumours"*

6.5.2 Electrocardiogram

Descriptive summaries of ECG findings at baseline and throughout the study will be generated. The number and percentage of patients with abnormal ECG findings at baseline or new on-treatment ECG changes (e.g., QTc prolongation, presence of U waves) will be summarized.

6.5.3 Laboratory Tests

Descriptive summaries of laboratory values at baseline and throughout the study will be generated and listed on the basis of a graded scale for selected parameters. For these selected parameters, changes from baseline and the proportion of patients experiencing clinically significant changes relative to baseline will be summarized by treatment arm.

The number and percentage of patients with positive serum antibodies to lebrikizumab at baseline and during the study will be tabulated.

6.5.4 Vital Signs

Descriptive summaries of vital signs, including the change from baseline for vital signs, will be generated by treatment arm. Vital signs include respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature.

6.6 PHARMACOKINETIC ANALYSES

Individual and mean serum lebrikizumab concentration–versus–time data will be reported. *During the treatment period*, mean concentrations will be reported at Weeks 4, 12, 24, 36, and 52 ($C_{\min, Wk4}$, $C_{\min, Wk12}$, $C_{\min, Wk24}$, $C_{\min, Wk36}$, C_{Wk52} , respectively). Estimates for these parameters will be tabulated and summarized (mean, SD, coefficient of variation, median, minimum, and maximum). Additional PK analyses during the treatment period or the safety follow-up period may be conducted as appropriate. Population PK

modeling may be performed to characterize inter-individual variability, which may be reported separately from the clinical study report.

6.7 EXPLORATORY ANALYSES

Analysis of exploratory efficacy endpoints will be described in the SAP.

Several pharmacodynamic biomarkers have been identified (e.g., periostin, CCL18, YKL40, COMP, OPN, CCL13) and will be measured in serum or plasma samples to assess the effect of lebrikizumab on these biomarkers. Exploratory exposure-response analysis will be performed as appropriate.

6.7.1 High-Resolution, Thin-Section Computed Tomography Quantitative Scores

Baseline HRCT images will be performed using a low-dose radiation protocol (see study- and site-specific HRCT guidance manual). Additionally, an optional HRCT scan will be performed at Week 52 for patients enrolled at sites located in the United States. Scans obtained from those at Week 52 will be centrally reviewed and scored for changes in lung fibrosis on the basis of quantitative computer tomography. Changes in quantitative computer tomography scores will be calculated as an exploratory endpoint and assessed relative to disease progression, spirometry parameters, and other efficacy measures.

6.8 OPTIONAL INTERIM ANALYSES

The Sponsor may choose to conduct up to two interim efficacy analyses. Interim analyses will involve unblinding of treatment assignments to the Sponsor for purposes of data analysis and interpretation. Patients and all study site personnel will remain blinded to individual patient-level treatment assignments until completion of the trials. The decision to conduct optional interim analyses and the timing of the analyses will be documented in the Sponsor's trial master file prior to the conduct of the interim analyses. The interim analyses 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.

After the analysis of Cohort A, the Sponsor formed an IMC to perform an unplanned interim futility analysis of Cohort B to determine if it should be terminated for lack of sufficient efficacy. Following this analysis, the decision was made to continue the study and not perform additional efficacy and/or futility interim analyses.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

Roche will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC with use of eCRFs. Sites

will be responsible for data entry into the EDC system. In the event of discrepant data, Roche will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

Roche will produce EDC study specifications that describe the quality checking to be performed on the data. Central laboratory data and spirometry data will be sent directly to Roche, with use of the Roche'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.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using 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 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, PROs, 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 7.5.

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

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational 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.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMPs, including eCRFs, ICFs, 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. Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws. Studies conducted in the EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample ICF (and ancillary sample ICFs such as a Child's Assent or Caregiver's ICF, if applicable) 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 ICFs or any alternate consent forms proposed by the site (collectively, the "consent forms") before IRB/IEC submission. The final IRB/IEC-approved consent forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each patient the objectives of the exploratory research. 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 allow any remaining specimens to be used for exploratory research. Patients who decline to participate will not need to provide a separate signature.

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/IEC-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/IEC 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 or the patient's legally authorized representative. 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 ICFs, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/IEC by the Principal Investigator and reviewed and approved by the IRB/IEC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/IEC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. Investigators are also responsible for promptly informing the IRB/IEC of any protocol amendments (see Section 9.5).

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/IEC. 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/IEC, and archived in the site's study file.

8.4 CONFIDENTIALITY

Roche 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 Roche location.

Patient medical information obtained by this study is confidential and may be disclosed only to third parties as permitted by the ICF (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 FDA and other national and local health authorities; Roche monitors, representatives, and collaborators, and the IRB/IEC 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, ICFs, and documentation of IRB/IEC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, which include an audit trail containing a complete record of all changes to data.

9.2 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/IECs to inspect facilities and records relevant to this study.

9.3 ADMINISTRATIVE STRUCTURE

This study is sponsored by F. Hoffmann-La Roche Ltd. A total of 120 international study centers *have participated* in this study *and enrolled 507* patients. Roche will provide clinical operations oversight, data management support, and medical monitoring. The eCRF data will be recorded via a Sponsor-designated EDC system. An IxRS will be used for study drug inventory management and to randomize patients to study drug. Spirometry will be transmitted to a central spirometry center. Blood samples will be sent to central laboratory for analysis. Serum samples for PK and PD analysis will be sent to a central laboratory for sample storage. Sample analysis will be performed by an external vendor or the Sponsor.

An iDMC will be set up to monitor the safety of the study.

9.4 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to Roche prior to submission. This allows Roche to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

Roche will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, Roche 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 Roche personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Roche personnel.

Any inventions and resulting patents, improvements, 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.

9.5 PROTOCOL AMENDMENTS

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

Approval must be obtained from the IRB/IEC 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 and Placebo Controlled Treatment Period - Cohort A

	Screening	Rand.	Placebo Controlled Study Treatment Period ^a														EOT ^{a, b}	ET ^a	UV
Week	—	0	1	4	8	12	16	20	24	28	32	36	40	44	48	52	—	—	
Day (Window)	-28	1	8 (±2)	29 (±3)	57 (±3)	85 (±3)	113 (±3)	141 (±3)	169 (±3)	197 (±3)	225 (±3)	253 (±3)	281 (±3)	309 (±3)	337 (±3)	365 (±3)	—	—	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	—	—	
Informed consent ^c	x																		
Demographic data	x																		
Medical history	x																		
Physical exam ^d	x																		
Limited physical examination ^d		x														x	x	x	
Weight	x					x			x			x			x	x	x		
Height	x																		
Vital signs ^e	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Resting pulse oximetry	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Single ECG ^f	x								x							x	x		
Spirometry	x ^g	x	x	x		x			x			x		x		x	x	x	
DL _{CO} (mL CO/min-1/mmHg-1)	x	x	x	x		x			x			x		x		x	x	x	
HRCT ± SLB central review for eligibility ^h	x																		
Quantitative HRCT ⁱ	x															x	x		

Appendix 1
Schedule of Assessments: Screening and Placebo Controlled Treatment Period - Cohort A (cont.)

	Screening	Rand.	Placebo Controlled Study Treatment Period ^a													EOT ^{a, b}	ET ^a	UV
Week	—	0	1	4	8	12	16	20	24	28	32	36	40	44	48	52	—	—
Day (Window)	-28	1	8 (±2)	29 (±3)	57 (±3)	85 (±3)	113 (±3)	141 (±3)	169 (±3)	197 (±3)	225 (±3)	253 (±3)	281 (±3)	309 (±3)	337 (±3)	365 (±3)	—	—
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	—	—
6MWT/Borg CR10 Scale ⁱ	x	x							x							x	x	
ATAQ-IPF ^k		x		x		x			x			x				x	x	
SGRQ ^k		x		x		x			x			x				x	x	
EQ-5D ^k		x		x		x			x			x				x	x	x
Hematology ^l	x	x		x	x	x			x			x			x	x	x	x
Chemistry ^m	x	x		x	x	x			x			x			x	x	x	x
B-type natriuretic peptide	x																	
Urinalysis ⁿ	x	x				x			x			x				x	x	
Serum pregnancy test ^o	x																	
Urine pregnancy test ^o		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Serum PK sample ^p		x	x	x		x			x			x				x	x	
Plasma PD sample ^{p, q}		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum PD sample ^{p, q}	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 1

Schedule of Assessments: Screening and Placebo Controlled Treatment Period - Cohort A (cont.)

	Screening	Rand.	Placebo Controlled Study Treatment Period ^a													EOT ^{a, b}	ET ^a	UV
Week	—	0	1	4	8	12	16	20	24	28	32	36	40	44	48	52	—	—
Day (Window)	-28	1	8 (±2)	29 (±3)	57 (±3)	85 (±3)	113 (±3)	141 (±3)	169 (±3)	197 (±3)	225 (±3)	253 (±3)	281 (±3)	309 (±3)	337 (±3)	365 (±3)	—	—
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	—	—
Serum antibodies ^p		x		x		x			x			x				x	x	
Serum tryptase ^r																		
Optional DNA sample ^s		x																
Optional RNA sample ^s		x	x						x							x		
Study drug administration ^t		x ^r		x ^r	x ^r	x	x	x	x	x	x	x	x	x	x			
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events ^{d, u}	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Notes: On treatment days, all assessments should be performed prior to dosing unless otherwise specified.

6MWT=6-minute walk test; ATAQ-IPF=A Tool to Assess Quality of Life in IPF; Borg CR10=Borg Category Ratio 10 Scale[®]; DL_{CO}=diffusion capacity of the lung for carbon monoxide; ECG=electrocardiogram; EOT=end of treatment; EQ-5D=EuroQol 5-Dimension Questionnaire; ET=early termination; HRCT=high-resolution computed tomography; IPF=idiopathic pulmonary fibrosis; Rand.=randomization; SGRQ=St George's Respiratory Questionnaire; UV=unscheduled visit.

^a Patients who discontinue study drug are encouraged to remain in the study and complete all scheduled assessments. If this is not feasible, the patient should enter and complete the safety follow-up period or the early termination assessments, unless consent has been withdrawn. If a patient is unable or unwilling to complete the assessment for 6MWT and/or the qHRCT substudy assessment this will not be considered a protocol deviation.

^b Patients who enter the open label lebrikizumab treatment period should complete Day1 OL visit 35 on the same day.

Appendix 1

Schedule of Assessments: Screening and Placebo Controlled Treatment Period - Cohort A (cont.)

- ^c Informed consent may be obtained on the day of Visit 1 or prior to visit 1 at the discretion of the investigator. The informed consent process must be completed before initiating any Visit 1 assessments.
- ^d Record abnormalities observed at baseline on the Medical History and Baseline Conditions eCRF. New or worsening abnormalities should be recorded on the Adverse Event eCRF.
- ^e Respiratory rate, pulse rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature.
- ^f ECGs should be performed prior to any scheduled study procedures (e.g., vital sign measurements, blood draws, and study drug administration, if applicable).
- ^g Both pre- and post-bronchodilator testing are required at screening, but only pre-bronchodilator pulmonary function test is required throughout other study visits.
- ^h A Multidisciplinary Discussion of Diagnosis (MDD) based on 2011 ATS/ERS/JRS/ALAT guidelines will be utilized to finalize the diagnosis in the event the initial central review outcome results for HRCT and SLB are disparate (inconsistent with usual interstitial pneumonitis (UIP)/definite UIP).
- ⁱ Optional procedure for patients who have consented to participate in the HRCT substudy limited to the United States and selected countries. Baseline qHRCT scan does not need to be repeated if one was performed as part of the eligibility assessment. All patients enrolled in the substudy will have an additional qHRCT scan performed at the EoT Visit 16 at Week 52. Assessment at ET is requested but not considered a protocol deviation if the patient is unable or unwilling to perform.
- ^j The Borg CR10 Scale will be performed immediately before and after the 6MWT. Assessment of the 6MWT and Borg CR10 Scale at ET is requested but not considered a protocol deviation if the patient is unable or unwilling to perform.
- ^k Complete before all other non-PRO assessments and before the patient receives any disease-status information or study treatment during the study visit.
- ^l Includes RBC count, WBC count, hemoglobin, hematocrit, platelet count, and WBC differential count (neutrophils, bands, lymphocytes, eosinophils, basophils, monocytes, and other cells).
- ^m Includes sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase, creatinine phosphokinase, and uric acid. **Any patient who starts rescue therapy (including but not limited to pirfenidone) will need monitoring per the prescribing information.** All safety laboratory assessments, including those required for the prescribed rescue medication, should be analyzed by the central laboratory utilized for the GB28547 clinical study.
- ⁿ Includes protein, blood, glucose, and microscopic examination (RBC, WBC, casts, and crystals).
- ^o Only for women of childbearing potential see [Appendix 9](#).

Appendix 1

Schedule of Assessments: Screening and Placebo Controlled Treatment Period - Cohort A (cont.)

- ^p On dosing days. Samples for serum PK, PD, antibody (including anti-therapeutic antibody), and optional PAXgene mRNA analysis will be taken prior to dosing. An additional sample for serum antibody and PK analysis must be taken in the event of an anaphylactic, anaphylactoid, or serious hypersensitivity reaction. PLB2 antibody testing may be performed as appropriate using serum samples collected at pre-specified timepoints.
- ^q Includes IL-13– or IPF-related biomarkers (e.g., periostin, CCL18, YKL40, COMP, OPN, CCL13). Screening serum periostin sample should be collected and shipped to the central laboratory within the first 2 weeks of screening.
- ^r Whenever possible, patients who experience an acute onset of symptoms of an anaphylactic, anaphylactoid, or serious hypersensitivity reaction should have a blood sample for total serum tryptase analysis collected 1–6 hours after the event. The tryptase sample will be collected and analyzed per the site's local laboratory practice.
- ^s The DNA sample and whole blood PAXgene mRNA samples are optional and should be obtained only from patients who sign the separate RCR Informed Consent Form.
- ^t Patients will remain in the clinic for 1 hour after dosing for the first three dosing visits and for 30 minutes after dosing on all other study drug administration days for routine safety monitoring.
- ^u All adverse events including serious adverse events and adverse events of special interest.

Appendix 2

Schedule of Assessments: Open-Label Lebrizumab Treatment Period - Cohort A

Week	Wk 52 (Day1 OL)	Wk 56 (Wk4 OL)	Wk 60 (Wk8 OL)	Wk 64 (Wk12 OL)	Wk 68 (Wk16 OL)	Wk 72 (Wk20 OL)	Wk 76 (Wk24 OL)	Wk 80 (Wk28 OL)	Wk84 (Wk32 OL)	Wk 88 (Wk36 OL)	Wk92 (Wk40 OL)	Wk96 (Wk44 OL)	Wk100 (Wk48 OL)	Wk104 (Wk52 OL)		
Day (Assessment Window)	365 (1OL) (± 3)	393 (29OL) (± 3)	421 (57OL) (± 3)	449 (85OL) (± 3)	477 (13OL) (± 3)	505 (141 OL) (± 3)	533 (169 OL) (± 3)	561 (197 OL) (± 3)	589 (225 OL) (± 3)	617 (253 OL) (± 3)	645 (281 OL) (± 3)	673 (309 OL) (± 3)	701 (337 OL) (± 3)	729 (365 OL) (± 3)		
Visit	35	36	37	38	39	40	41	42	43	44	45	46	47	EoT ^b /SFU Wk4	ET ^q	UV
Limited physical exam ^a														x	x	x
Weight				x			x			x				x	x	
Vital signs ^c		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Resting Pulse Oximetry		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Single ECG ^d														x	x	
Spirometry		x	x	x			x			x			x	x	x	x
DLco		x	x	x			x			x			x	x	x	x
6MWT/BorgCR10 ^e							x							x	x	
ATAQ-PF ^f							x							x	x	
SGRQ ^f							x							x	x	
EQ-5D ^f							x							x	x	x

Appendix 2

Schedule of Assessments: Open-Label Lebrikizumab Treatment Period - Cohort A (cont.)

Week	Wk 52 (Day1 OL)	Wk 56 (Wk4 OL)	Wk 60 (Wk8 OL)	Wk 64 (Wk12 OL)	Wk 68 (Wk16 OL)	Wk 72 (Wk20 OL)	Wk 76 (Wk24 OL)	Wk 80 (Wk28 OL)	Wk84 (Wk32 OL)	Wk 88 (Wk36 OL)	Wk92 (Wk40 OL)	Wk96 (Wk44 OL)	Wk100 (Wk48 OL)	Wk104 (Wk52 OL)		
Day (Assessment Window)	365 (1OL) (± 3)	393 (29OL) (± 3)	421 (57OL) (± 3)	449 (85OL) (± 3)	477 (13OL) (± 3)	505 (141 OL) (± 3)	533 (169 OL) (± 3)	561 (197 OL) (± 3)	589 (225 OL) (± 3)	617 (253 OL) (± 3)	645 (281 OL) (± 3)	673 (309 OL) (± 3)	701 (337 OL) (± 3)	729 (365 OL) (± 3)		
Visit	35	36	37	38	39	40	41	42	43	44	45	46	47	EoT ^b /SFU Wk4	ET ^q	UV
Hematology ^g		x	x		x		x		x		x		x	x	x	x
Chemistry ^h		x	x		x		x		x		x		x	x	x	x
Urinalysis ⁱ		x	x		x		x		x		x		x	x	x	
Urine pregnancy ^j		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Serum PK ^k				x			x			x				x	x	
Plasma PD sample ^{k,l}		x	x	x			x			x			x	x	x	x
Serum PD ^{k,l}		x	x	x			x			x			x	x	x	x
Serum antibodies ^k		x		x			x							x	x	
Serum Tryptase ^m																
Optional RNA ⁿ				x			x							x		
Study drug administration ^{o,p}	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Concomitant medications ^q		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 2

Schedule of Assessments: Open-Label Lebrikizumab Treatment Period - Cohort A (cont.)

Week	Wk 52 (Day1 OL)	Wk 56 (Wk4 OL)	Wk 60 (Wk8 OL)	Wk 64 (Wk12 OL)	Wk 68 (Wk16 OL)	Wk 72 (Wk20 OL)	Wk 76 (Wk24 OL)	Wk 80 (Wk28 OL)	Wk84 (Wk32 OL)	Wk 88 (Wk36 OL)	Wk92 (Wk40 OL)	Wk96 (Wk44 OL)	Wk100 (Wk48 OL)	Wk104 (Wk52 OL)		
Day (Assessment Window)	365 (1OL) (± 3)	393 (29OL) (± 3)	421 (57OL) (± 3)	449 (85OL) (± 3)	477 (13OL) (± 3)	505 (141 OL) (± 3)	533 (169 OL) (± 3)	561 (197 OL) (± 3)	589 (225 OL) (± 3)	617 (253 OL) (± 3)	645 (281 OL) (± 3)	673 (309 OL) (± 3)	701 (337 OL) (± 3)	729 (365 OL) (± 3)		
Visit	35	36	37	38	39	40	41	42	43	44	45	46	47	EoT ^b /SFU Wk4	ET ^d	UV
Adverse events ^{a,q}		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

6MWT=six minute walk test; ATAQ-IPF= A Tool to Assess Quality of Life in IPF; Borg CR10 Scale = Borg Category Ratio 10 Scale[®]; CTD=connective-tissue disease; DL_{CO}=diffusion capacity of the lung for carbon monoxide; eCRF=electronic Case Report Form; EOMT=end of minimum treatment; EOT=end of treatment; EQ-5D=EuroQol 5-Dimension Questionnaire; ET=early termination; FEV₁=forced expiratory volume in 1 second; FVC=forced vital capacity; HRCT=high-resolution computed tomography; IL-13=interleukin 13; IPF=idiopathic pulmonary fibrosis; PD=pharmacodynamic; PK=pharmacokinetic; Rand.=Randomization; SGRQ=St. George's Respiratory Questionnaire; UV=unscheduled visit.

Notes: On treatment days, all assessments should be performed prior to dosing unless otherwise specified.

^a New or worsening abnormalities should be recorded on the Adverse Event eCRF.

^b This visit replaces Safety Follow-up Visit 1 on [Appendix 4](#). The next visit is Safety Follow-up Visit 2 at Week 12 (12 weeks after last dose of study drug).

^c Respiratory rate, pulse rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

^d ECGs should be performed prior to any scheduled study procedures (e.g., vital sign measurements, blood draws, and study drug administration, if applicable).

^e The Borg CR10 Scale will be performed immediately before and after the 6MWT.

^f Complete before all other non-PRO assessments and before the patient receives any disease-status information or study treatment during the study visit.

Appendix 2

Schedule of Assessments: Open-Label Lebrikizumab Treatment Period - Cohort A (cont.)

- ^g Includes RBC count, WBC count, hemoglobin, hematocrit, platelet count, and WBC differential count (neutrophils, bands, lymphocytes, eosinophils, basophils, monocytes, and other cells).
- ^h Includes sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase, creatinine phosphokinase, and uric acid. Any patient who starts rescue therapy (including but not limited to pirfenidone) will need monitoring per the prescribing information. All safety laboratory assessments, including those required for the prescribed rescue medication, should be analyzed by the central laboratory utilized for the GB28547 clinical study.
- ⁱ Includes protein, blood, glucose, and microscopic examination (RBC, WBC, casts, and crystals).
- ^j Only for women of childbearing potential see [Appendix 9](#).
- ^k On dosing days. Samples for serum PK, PD, antibody (including anti-therapeutic antibody), and optional PAXgene mRNA analysis will be taken prior to dosing. An additional sample for serum antibody and PK analysis must be taken in the event of an anaphylactic, anaphylactoid, or serious hypersensitivity reaction. PLB2 antibody testing may be performed as appropriate using serum samples collected at pre-specified timepoints.
- ^l Includes IL-13 or IPF-related biomarkers (e.g., periostin, CCL18, YKL40, COMP, OPN, CCL13).
- ^m Whenever possible, patients who experience an acute onset of symptoms of an anaphylactic, anaphylactoid, or serious hypersensitivity reaction should have a blood sample for total serum tryptase analysis collected 1–6 hours after the event. The tryptase sample will be collected and analyzed per the site's local laboratory practice.
- ⁿ The whole blood PAXgene mRNA samples are optional and should be obtained only from patients who sign the separate RCR Informed Consent Form.
- ^o Patients will remain in the clinic for 1 hour after dosing for the first three dosing visits and for 30 minutes after dosing on all other study drug administration days for routine safety monitoring.
- ^p Patients who discontinue study drug are encouraged to remain in the study and complete all scheduled assessments. If this is not feasible, the patient should enter and complete the safety follow-up period or the early termination assessments, unless consent has been withdrawn.
- ^q All adverse events including serious adverse events and adverse events of special interest.

Appendix 3
Schedule of Assessments: Screening, Pirfenidone Titration Run-In, and Placebo-Controlled Treatment Period - Cohort B

Week	Screening	PFD titration -run-in	Rand.	Placebo controlled Study Treatment Period ^a													EOT ^{a, b}	ET ^a	UV
				1	4	8	12	16	20	24	28	32	36	40	44	48			
Day (Window)	-28 (± 14)	4-6 wks (28-42 days)	1	8 (± 2)	29 (± 3)	57 (± 3)	85 (± 3)	113 (± 3)	141 (± 3)	169 (± 3)	197 (± 3)	225 (± 3)	253 (± 3)	281 (± 3)	309 (± 3)	337 (± 3)	365 (± 3)	—	—
Visit	1	1.5	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	—	—
Informed consent ^c	x																		
Demographic data	x																		
Medical history	x																		
Physical exam ^d	x																		
Limited physical examination ^d			x														x	x	x
Weight	x	x	x		x	x	x			x			x			x	x	x	
Height	x																		
Vital signs ^e	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Resting pulse oximetry	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Single ECG ^f	x									x							x	x	
Spirometry	x ^g		x	x	x		x			x			x		x		x	x	x

Appendix 3

Schedule of Assessments: Screening, Pirfenidone Titration Run-In, and Placebo-Controlled Treatment Period - Cohort B (cont)

	Screening	PFD titration -run-in	Rand.	Placebo controlled Study Treatment Period ^a													EOT ^{a, b}	ET ^a	UV
				0	1	4	8	12	16	20	24	28	32	36	40	44			
Week	—		0	1	4	8	12	16	20	24	28	32	36	40	44	48	52	—	—
Day (Window)	-28 (± 14)	4-6 wks (28-42 days)	1	8 (± 2)	29 (± 3)	57 (± 3)	85 (± 3)	113 (± 3)	141 (± 3)	169 (± 3)	197 (± 3)	225 (± 3)	253 (± 3)	281 (± 3)	309 (± 3)	337 (± 3)	365 (± 3)	—	—
Visit	1	1.5	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	—	—
DL _{co} (mL CO/min-1/m mHg-1)	x		x	x	x		x			x			x		x		x	x	x
HRCT ± SLB central review for eligibility ^h	x																		
Quantitative HRCT ⁱ	x																x	x	
6MWT/Borg CR10 Scale ^j	x		x							x							x	x	
ATAQ-IPF ^k	x	x	x		x		x			x			x				x	x	
SGRQ ^k	x	x	x		x		x			x			x				x	x	
EQ-5D ^k			x		x		x			x			x				x	x	x
Hematology ^l	x		x		x	x	x			x			x			x	x	x	x
Chemistry ^m	x	x ⁿ	x	x	x	x	x	x	x	x			x			x	x	x	x

Appendix 3
Schedule of Assessments: Screening, Pirfenidone Titration Run-In, and Placebo-Controlled Treatment Period - Cohort B (cont)

	Screening	PFD titration -run-in	Rand.	Placebo controlled Study Treatment Period ^a													EOT ^{a, b}	ET ^a	UV
				0	1	4	8	12	16	20	24	28	32	36	40	44			
Week	—		0	1	4	8	12	16	20	24	28	32	36	40	44	48	52	—	—
Day (Window)	-28 (± 14)	4-6 wks (28-42 days)	1	8 (± 2)	29 (± 3)	57 (± 3)	85 (± 3)	113 (± 3)	141 (± 3)	169 (± 3)	197 (± 3)	225 (± 3)	253 (± 3)	281 (± 3)	309 (± 3)	337 (± 3)	365 (± 3)	—	—
Visit	1	1.5	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	—	—
B-type natriuretic peptide	x																		
Urinalysis ^o	x		x				x			x			x				x	x	
Serum pregnancy test ^p	x																		
Urine pregnancy test ^p			x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum PK sample ^q			x	x	x		x			x			x				x	x	
Plasma PD sample ^{q, r}			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum PD sample ^{q, r}	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum antibodies ^q			x		x		x			x			x				x	x	

Appendix 3

Schedule of Assessments: Screening, Pirfenidone Titration Run-In, and Placebo-Controlled Treatment Period - Cohort B (cont)

Week	Screening	PFD titration -run-in	Rand.	Placebo controlled Study Treatment Period ^a													EOT ^{a, b}	ET ^a	UV
				1	4	8	12	16	20	24	28	32	36	40	44	48			
Day (Window)	-28 (± 14)	4-6 wks (28-42 days)	1	8 (± 2)	29 (± 3)	57 (± 3)	85 (± 3)	113 (± 3)	141 (± 3)	169 (± 3)	197 (± 3)	225 (± 3)	253 (± 3)	281 (± 3)	309 (± 3)	337 (± 3)	365 (± 3)	—	—
Visit	1	1.5	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	—	—
Serum tryptase ^s																			
Optional DNA sample ^t			x																
Optional RNA sample ^t			x	x						x							x		
Study drug administration ^u			x ^s		x ^s	x ^s	x	x	x	x	x	x	x	x	x	x			
PFD dispensing		x	x		x	x	x	x	x	x	x	x	x	x	x	x	x		
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events ^v	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

6MWT=6-minute walk test; ATAQ-IPF=A Tool to Assess Quality of Life in IPF; Borg CR10=Borg Category Ratio 10 Scale®; DL_{CO}=diffusion capacity of the lung for carbon monoxide; ECG=electrocardiogram; EOT=end of treatment; EQ-5D=EuroQol 5-Dimension Questionnaire; ET=early termination; HRCT=high-resolution computed tomography; IPF=idiopathic pulmonary fibrosis; PFD=pirfenidone, Rand. =randomization; SGRQ=St. George's Respiratory Questionnaire; UV=unscheduled visit.

Notes: On treatment days, all assessments should be performed prior to dosing unless otherwise specified.

Appendix 3

Schedule of Assessments: Screening, Pirfenidone Titration Run-In, and Placebo-Controlled Treatment Period - Cohort B (cont)

- ^a Patients who discontinue study drug are encouraged to remain in the study and complete all scheduled assessments. If a patient is unable or unwilling to complete the assessment for 6MWT and/or the qtHRCT substudy assessment this will not be considered a protocol deviation. If this is not feasible, the patient should enter and complete the safety follow-up period or the early termination assessments, unless consent has been withdrawn.
- ^b This visit replaces Safety Follow-up Visit 1 on [Appendix 4](#). The next visit is Safety Follow-up Visit 2 at Week 12.
- ^c Informed consent may be obtained on the day of Visit 1 or prior to visit 1 at the discretion of the investigator. The informed consent process must be completed before initiating any Visit 1 assessments.
- ^d Record abnormalities observed at baseline on the Medical History and Baseline Conditions eCRF. New or worsening abnormalities should be recorded on the Adverse Event eCRF.
- ^e Respiratory rate, pulse rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature.
- ^f ECGs should be performed prior to any scheduled study procedures (e.g., vital sign measurements, blood draws, and study drug administration, if applicable).
- ^g Both pre- and post-bronchodilator testing are required at screening, but only pre-bronchodilator pulmonary function test is required throughout other study visits.
- ^h A Multidisciplinary Discussion of Diagnosis (MDD) based on 2011 ATS/ERS/JRS/ALAT guidelines will be utilized to finalize the diagnosis in the event the initial central review outcome results for HRCT and SLB are disparate (inconsistent with usual interstitial pneumonitis (UIP)/definite UIP).
- ⁱ Optional procedure for patients who have consented to participate in the HRCT substudy limited to the United States. Baseline qtHRCT scan does not need to be repeated if one was performed as part of the eligibility assessment. All patients enrolled in the substudy will have an additional qtHRCT scan performed at the EOT Visit16 at Week 52. Assessment at ET visit is requested but not considered a protocol deviation if patient is unable or unwilling to perform.
- ^j The Borg CR10 Scale will be performed immediately before and after the 6MWT. Assessment of the 6MWT and Borg CR10 Scale at ET visit is requested but not considered a protocol deviation if patient is unable or unwilling to perform.
- ^k Complete before all other non-PRO assessments and before the patient receives any disease-status information or study treatment during the study visit.
- ^l Includes RBC count, WBC count, hemoglobin, hematocrit, platelet count, and WBC differential count (neutrophils, bands, lymphocytes, eosinophils, basophils, monocytes, and other cells).

Appendix 3

Schedule of Assessments: Screening, Pirfenidone Titration Run-In, and Placebo-Controlled Treatment Period - Cohort B (cont)

- ^m Includes sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase, creatinine phosphokinase, and uric acid. **Any patient who starts rescue therapy (including but not limited to pirfenidone) will need monitoring per the prescribing information. All safety laboratory assessments, including those required for the prescribed rescue medication, should be analyzed by the central laboratory utilized for the GB28547 clinical study.**
- ⁿ If run-in period exceeds 4 weeks, follow pirfenidone guidance provided in the ESBRIET/PIRESPA package insert for liver function test.
- ^o Includes protein, blood, glucose, and microscopic examination (RBC, WBC, casts, and crystals).
- ^p Only for women of childbearing potential see [Appendix 9](#).
- ^q On lebrikizumab dosing days. Samples for serum PK, PD, antibody (including anti-therapeutic antibody), and optional PAXgene mRNA analysis will be taken prior to lebrikizumab dosing. An additional sample for serum antibody and PK analysis must be taken in the event of an anaphylactic, anaphylactoid, or serious hypersensitivity reaction. *Anti*-PLB2 antibody testing may be performed as appropriate using serum samples collected at pre-specified timepoints.
- ^r Includes IL-13– or IPF-related biomarkers (e.g., periostin, CCL18, YKL40, COMP, OPN, CCL13). Screening serum periostin sample should be collected and shipped to the central laboratory within the first 2 weeks of screening.
- ^s Whenever possible, patients who experience an acute onset of symptoms of an anaphylactic, anaphylactoid, or serious hypersensitivity reaction should have a blood sample for total serum tryptase analysis collected 1–6 hours after the event. The tryptase sample will be collected and analyzed per the site’s local laboratory practice.
- ^t The DNA sample and whole blood PAXgene mRNA samples are optional and should be obtained only from patients who sign the separate RCR Informed Consent Form.
- ^u Patients will remain in the clinic for 1 hour after dosing for the first three dosing visits and for 30 minutes after dosing on all other study drug administration days for routine safety monitoring.
- ^v All adverse events including serious adverse events and adverse events of special interest.

Appendix 4 Schedule of Assessments: Safety Follow-Up Period

WEEK post last dose	4 ^a	12	18 (final visit)
Day post last dose (assessment window)	28 (± 3)	84 (± 3)	126 (± 3)
Visit	SFU1	SFU2	SFU3
Limited physical exam ^b	x		x
Weight	x		x
Vital signs ^c	x	x	x
Resting pulse oximetry	x	x	x
Single ECG (all patients) ^d	x		x
Spirometry ⁱ	x	x	x
DLco	x	x	x
6MWT/BorgCR10 ^e	x		
ATAQ-IPF ^f	x		x
SGRQ ^f	x		x
EQ-5D ^f	x		x
Hematology ^g	x	x	x
Chemistry ^h	x	x	x
Urinalysis ⁱ	x		
Urine pregnancy test ^j	x		
Serum PK sample ^k	x	x	x
Plasma PD sample ^{k,l}	x	x	x
Serum PD sample ^{k,l}	x	x	x
Serum antibodies ^k	x		x

Appendix 4 Schedule of Assessments: Safety Follow-Up Period (cont)

WEEK post last dose	4 ^a	12	18 (final visit)
Day post last dose (assessment window)	28 (± 3)	84 (± 3)	126 (± 3)
Visit	SFU1	SFU2	SFU3
Optional RNA sample ^m	x		
Concomitant medications	x	x	x
Adverse events ^{a,n}	x	x	x
PFD dispensing (Cohort B only)	x	x	

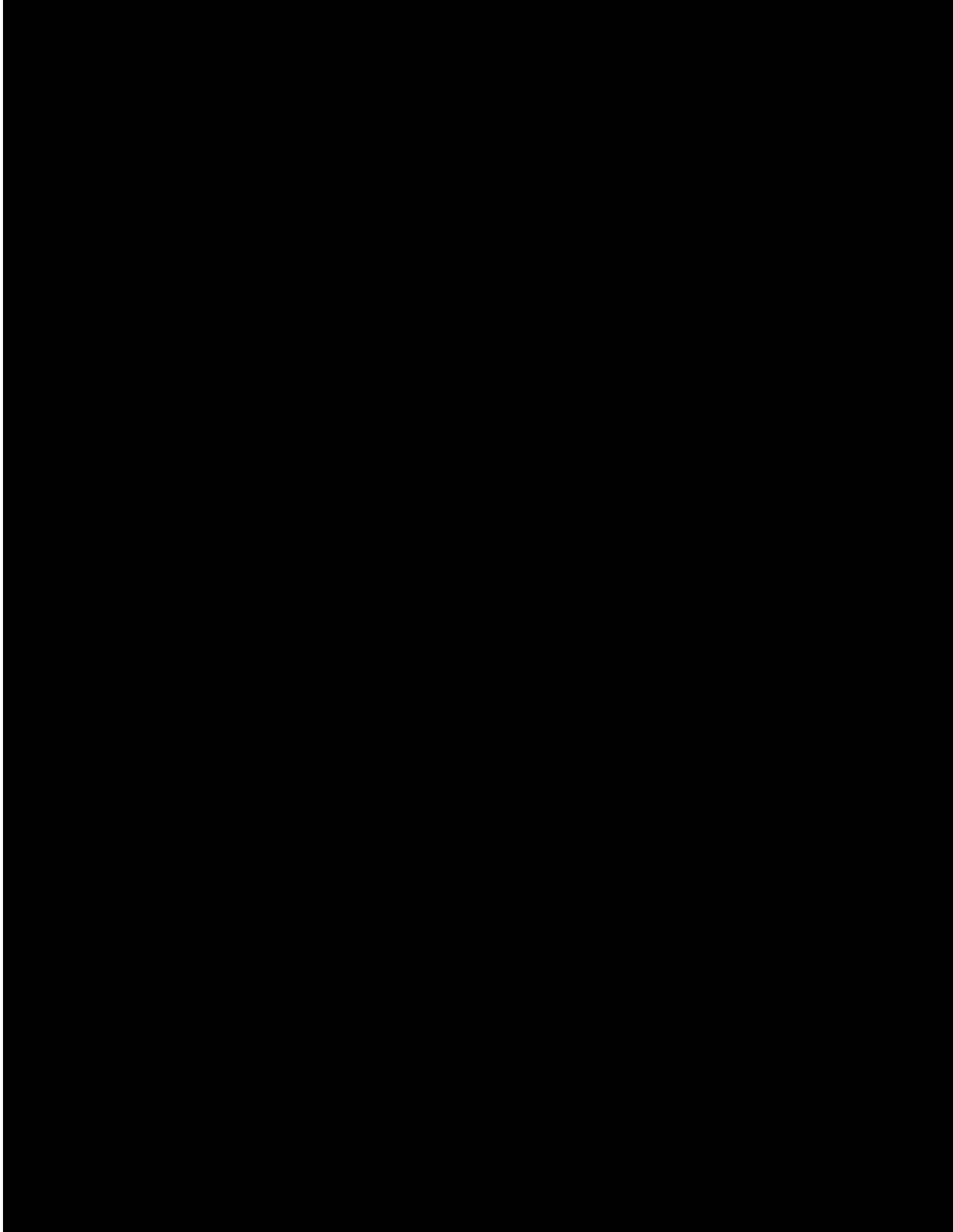
6MWT=6-minute walk test; ATAQ-IPF=A Tool to Assess Quality of Life in IPF; Borg CR10=Borg Category Ratio 10 Scale®; DL_{CO}=diffusion capacity of the lung for carbon monoxide; ECG=electrocardiogram; EOT=end of treatment; EQ-5D=EuroQol 5-Dimension Questionnaire; ET=early termination; HRCT=high-resolution computed tomography; IPF=idiopathic pulmonary fibrosis; SGRQ=St. George's Respiratory Questionnaire; UV=unscheduled visit.

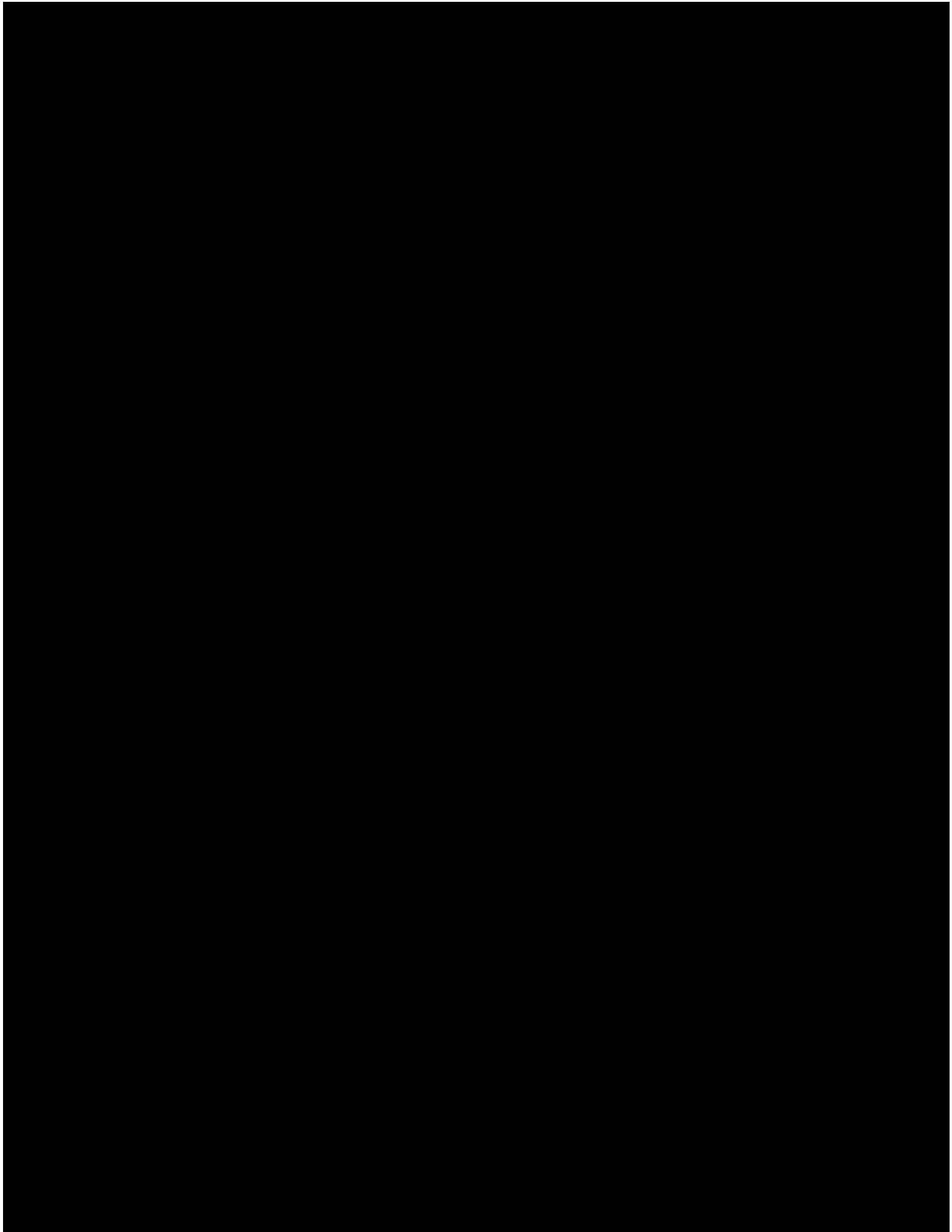
- ^a For patients in Cohort A who only complete the placebo controlled study period at Week 52 and choose to discontinue, the Week 52 visit will count as this visit. For patients in Cohort A who complete the open-label lebrizumab study period at week 52OL, the Week 52OL will count as this visit. For patients in Cohort B who complete the placebo controlled study period at Week 52, the Week 52 visit will count as this visit.
- ^b New or worsening abnormalities should be recorded on the Adverse Event eCRF.
- ^c Respiratory rate, pulse rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature.
- ^d ECGs should be performed prior to any scheduled study procedures (e.g., vital sign measurements, blood draws, and study drug administration, if applicable).
- ^e The Borg CR10 Scale will be performed immediately before and after the 6MWT.
- ^f Complete before all other non-PRO assessments and before the patient receives any disease-status information or study treatment during the study visit.
- ^g Includes RBC count, WBC count, hemoglobin, hematocrit, platelet count, and WBC differential count (neutrophils, bands, lymphocytes, eosinophils, basophils, monocytes, and other cells).

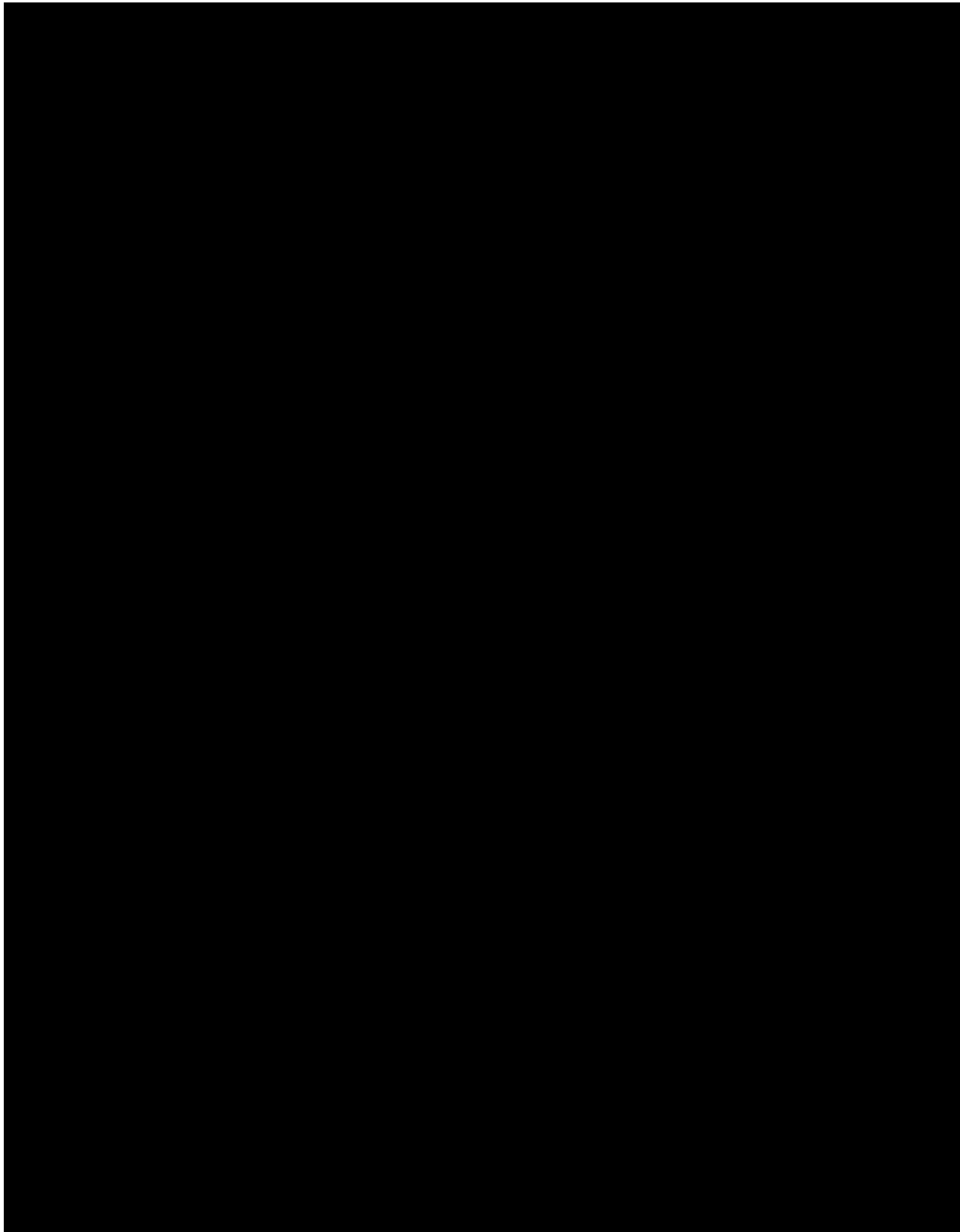
Appendix 4

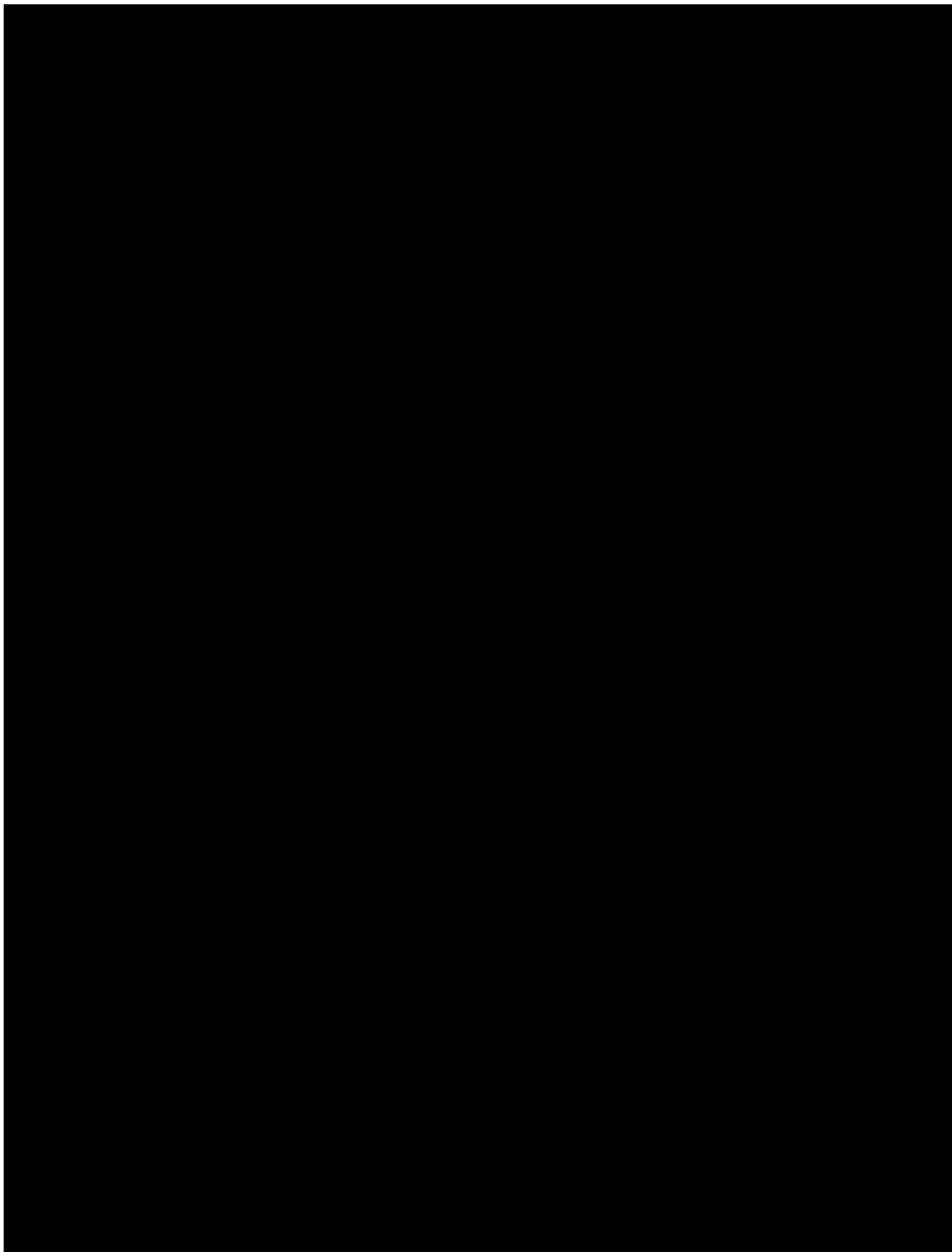
Schedule of Assessments: Safety Follow-Up Period (cont)

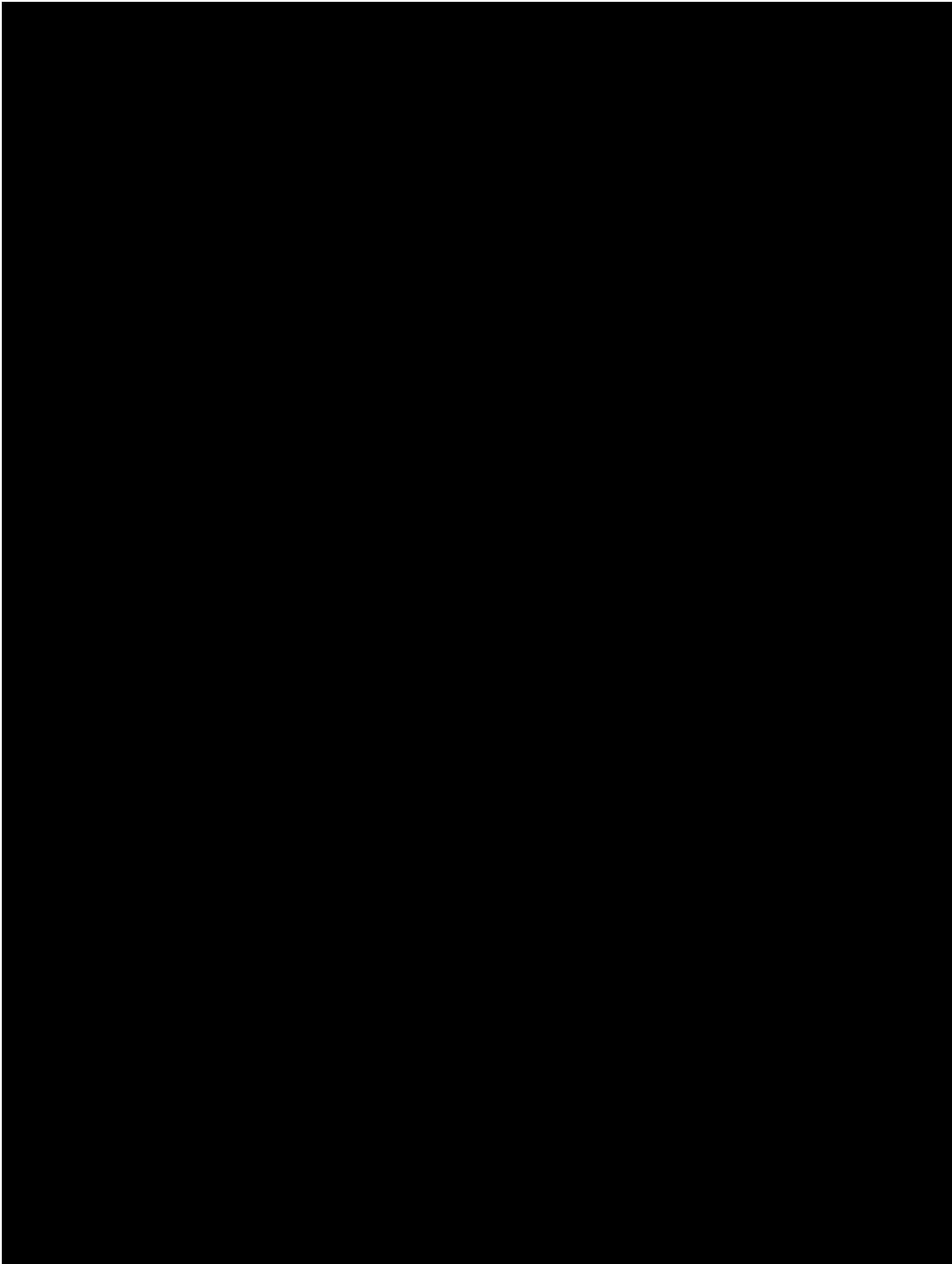
- ^h Includes sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase, creatinine phosphokinase, and uric acid. **Any patient who starts rescue therapy (including but not limited to pirfenidone) will need monitoring per the prescribing information.** All safety laboratory assessments, including those required for the prescribed rescue medication, should be analyzed by the central laboratory utilized for the GB28547 clinical study.
- ⁱ Includes protein, blood, glucose, and microscopic examination (RBC, WBC, casts, and crystals).
- ^j Only for women of childbearing potential see [Appendix 9](#).
- ^k On lebrikizumab dosing days. Samples for serum PK, PD, antibody (including anti-therapeutic antibody), and optional PAXgene mRNA analysis will be taken prior to lebrikizumab dosing. An additional sample for serum antibody and PK analysis must be taken in the event of an anaphylactic, anaphylactoid, or serious hypersensitivity reaction. *Anti*-PLB2 antibody testing may be performed as appropriate using serum samples collected at pre-specified timepoints.
- ^l Includes IL-13- or IPF-related biomarkers (e.g., periostin, CCL18, YKL40, COMP, OPN, CCL13).
- ^m The whole blood PAXgene mRNA samples are optional and should be obtained only from patients who sign the separate RCR Informed Consent Form.
- ⁿ All adverse events including serious adverse events and adverse events of special interest.

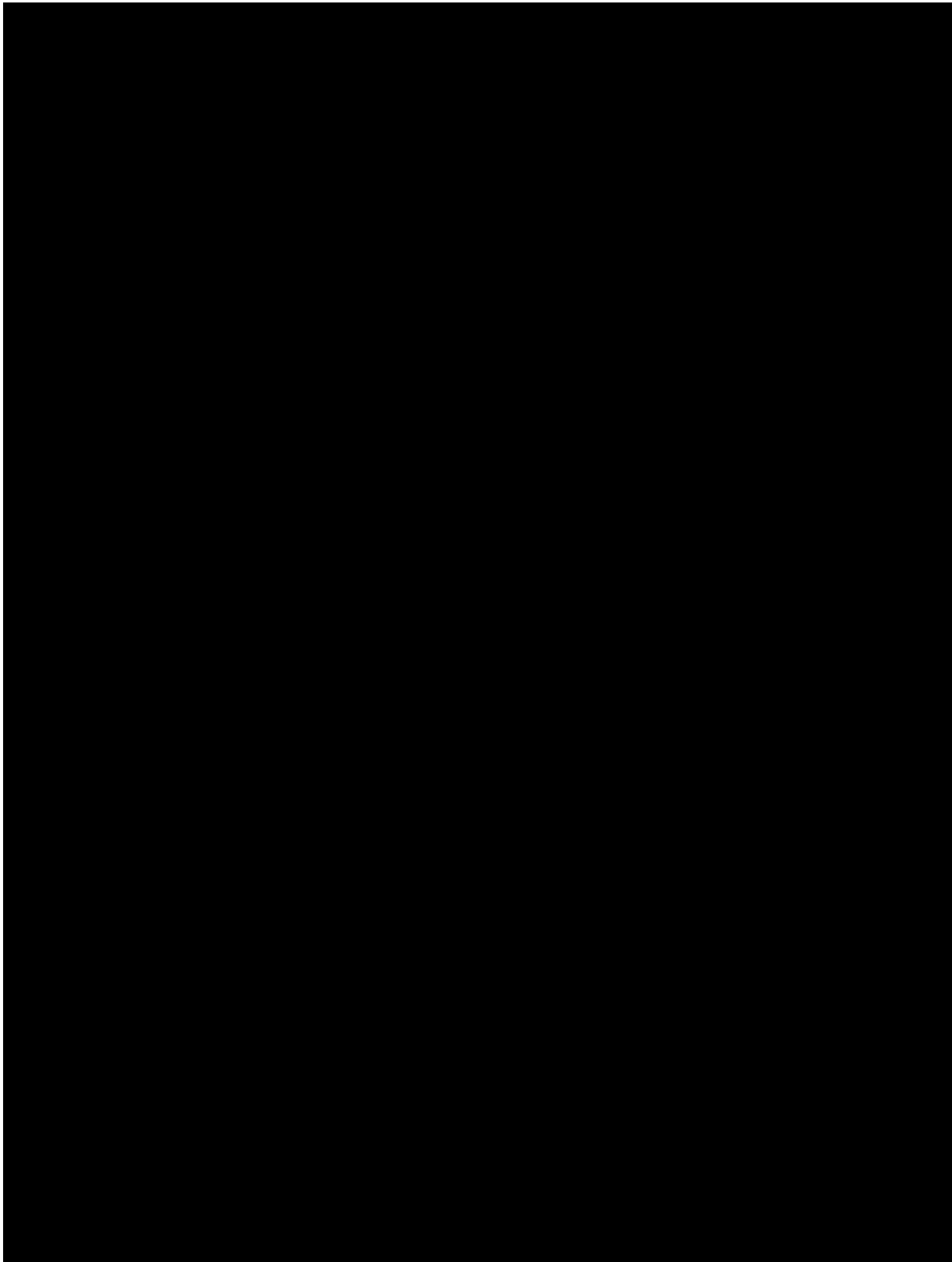


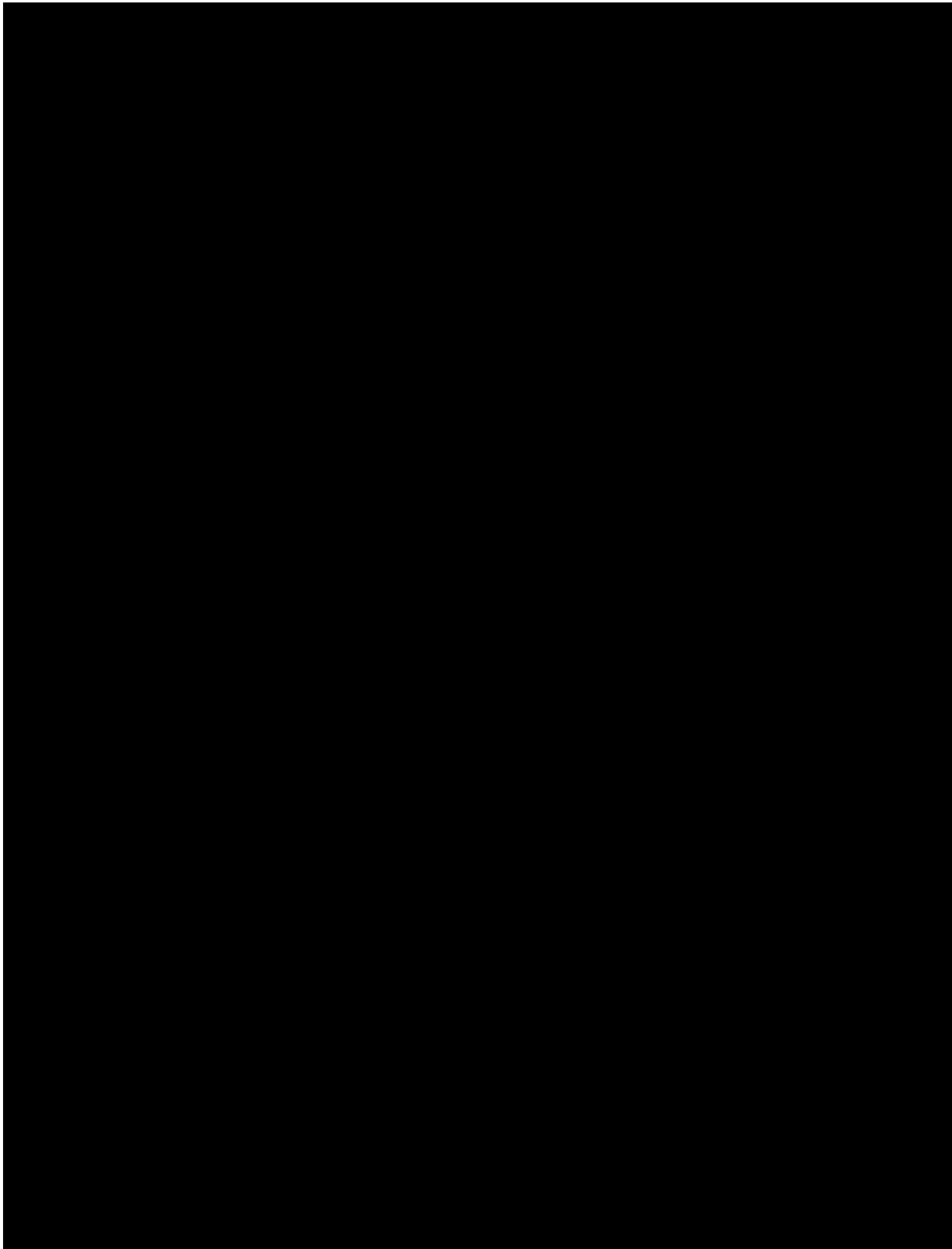


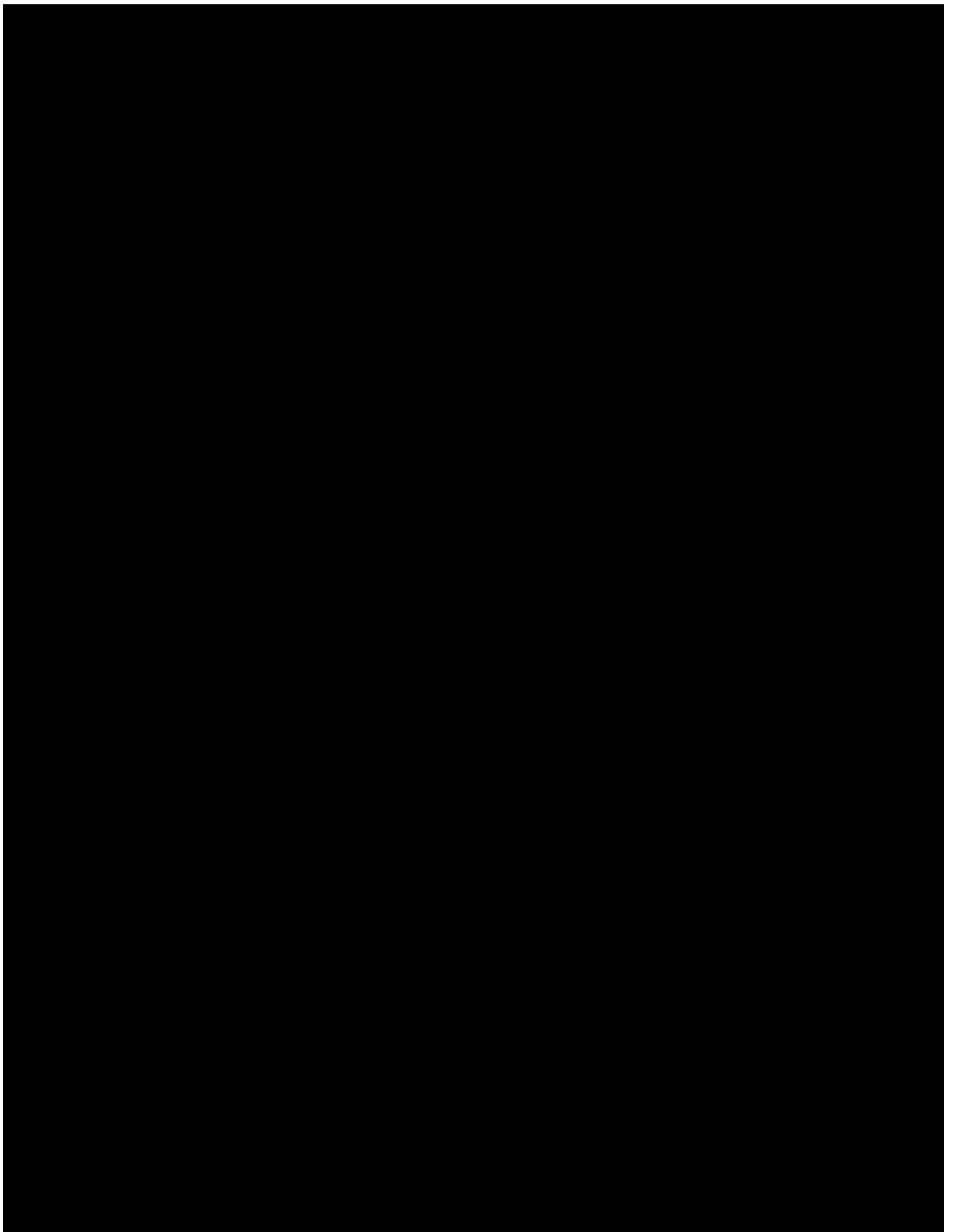


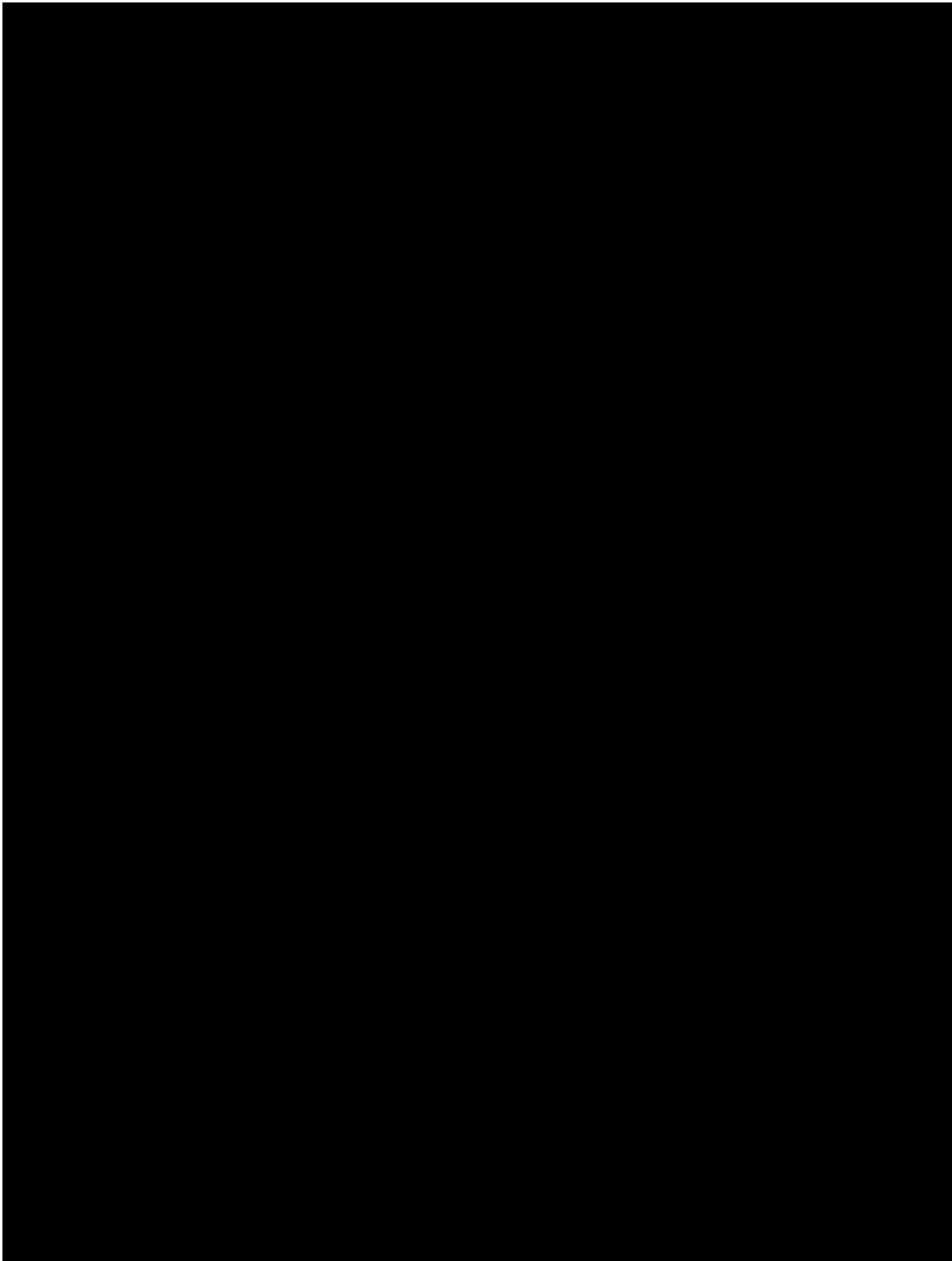


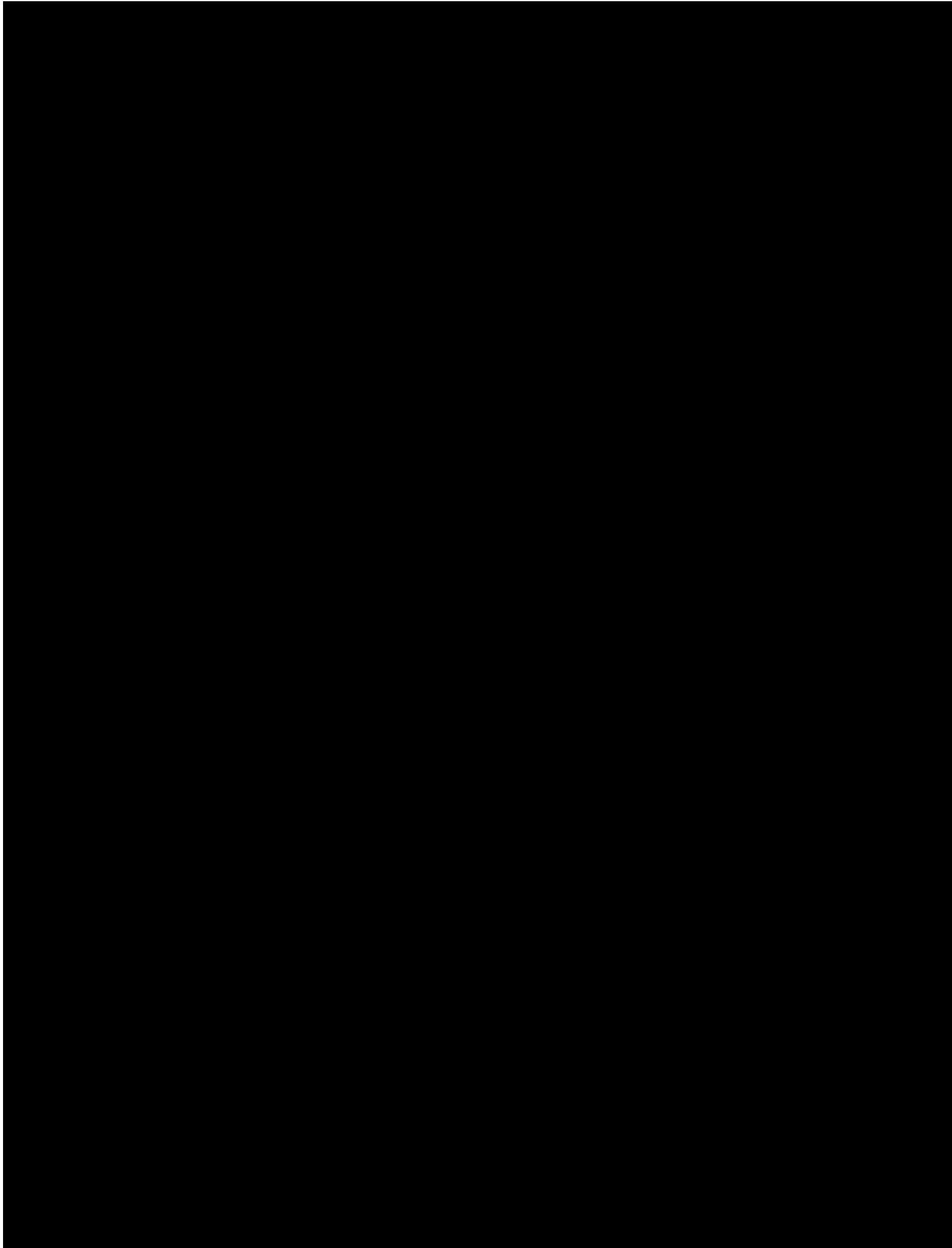


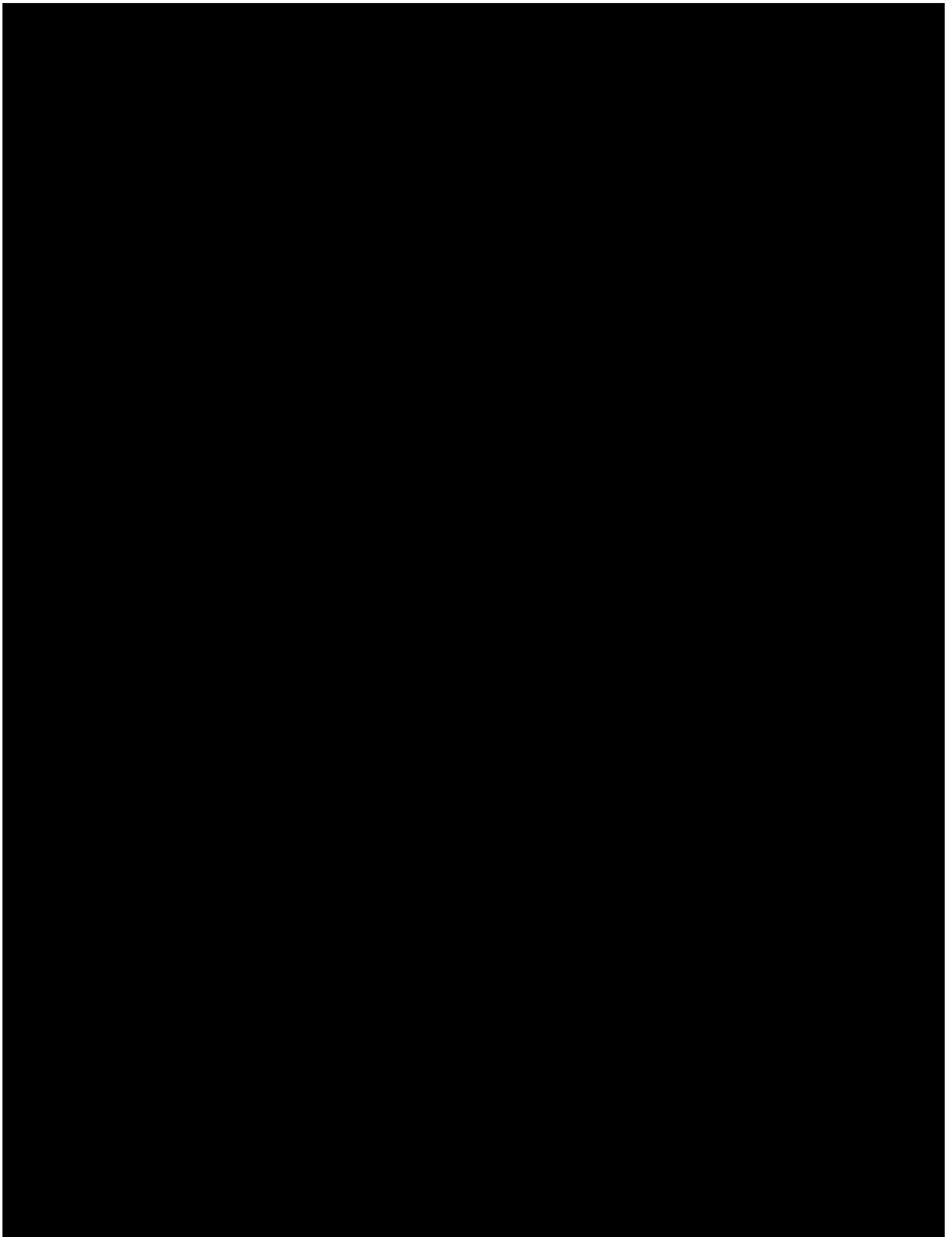


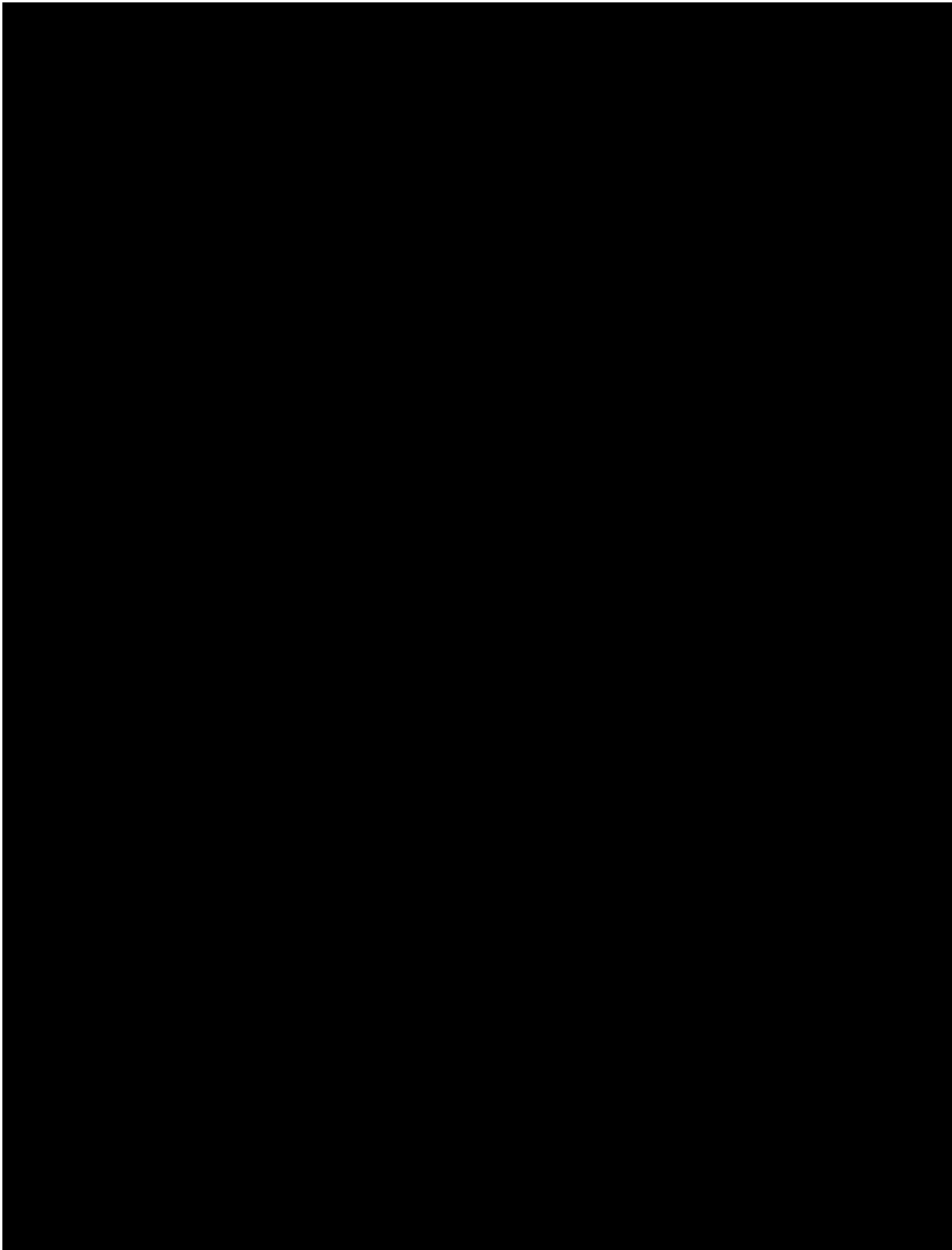


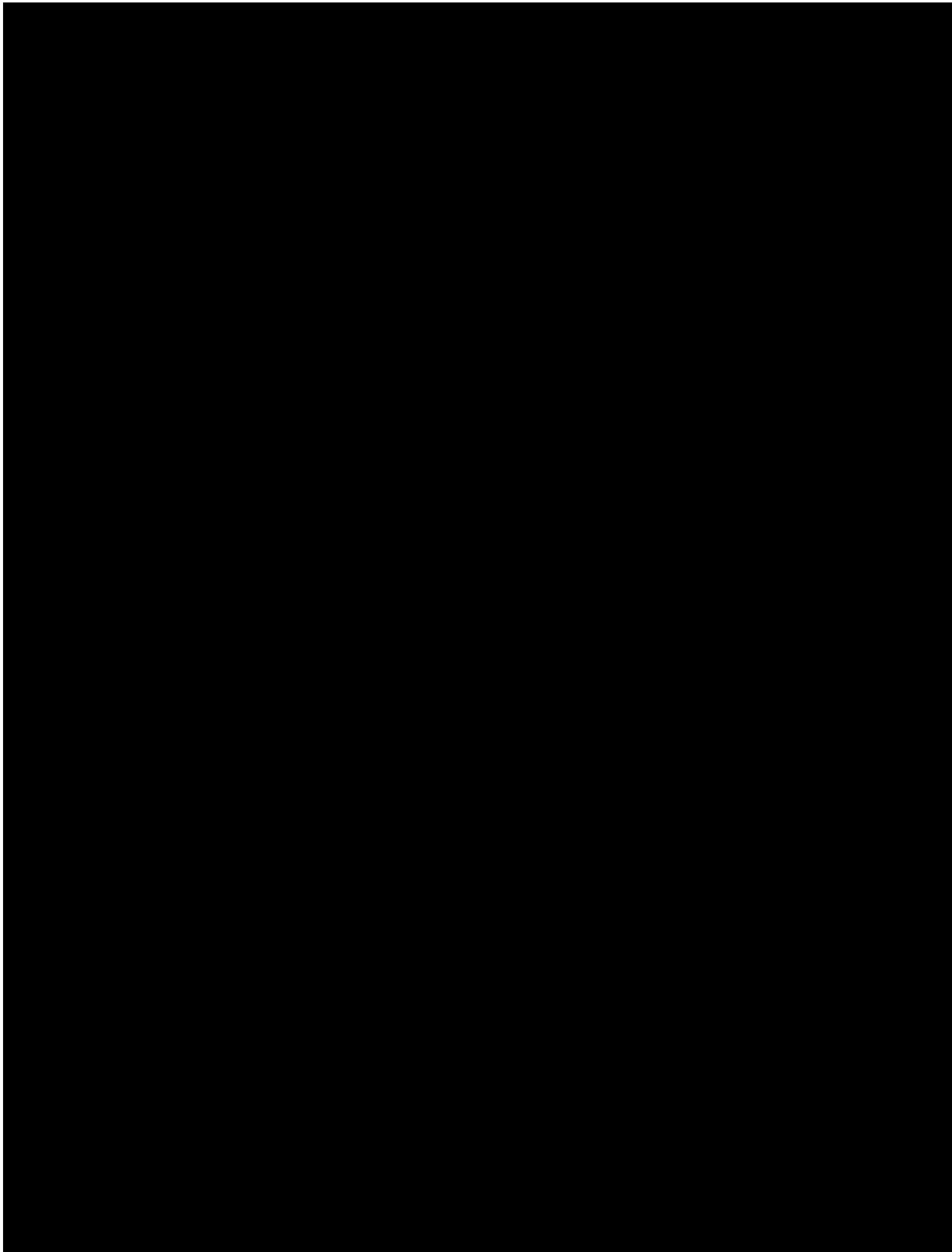


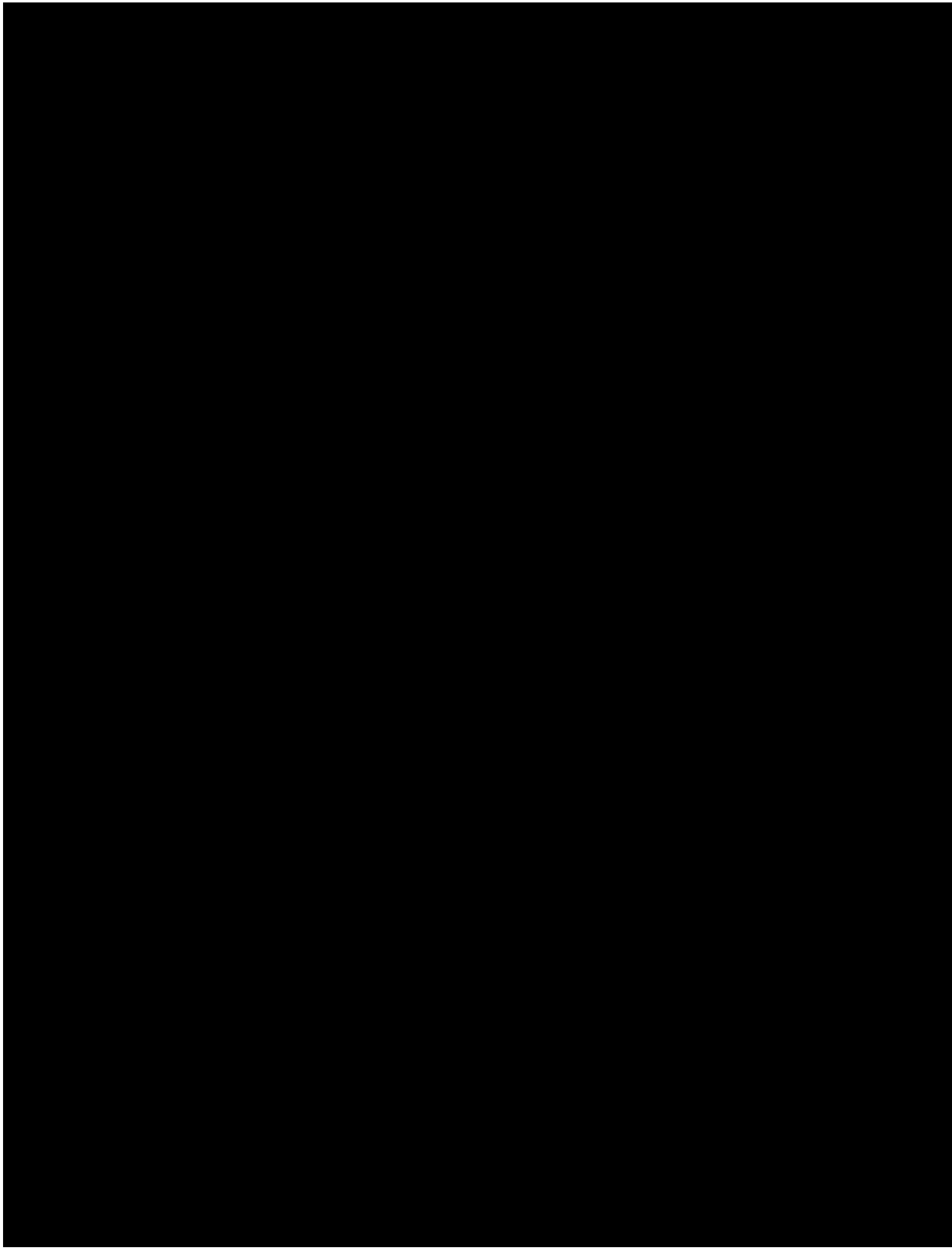












Appendix 8

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 ([Sampson et al. 2006](#)).

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

- 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)
 - 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)
 - 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 <90 mmHg or greater than 30% decrease from that person's baseline

Appendix 9

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 **unless** they meet one of the following criteria:

- The patient has been postmenopausal (amenorrheic) for at least 1 year
- The patient had a surgical bilateral oophorectomy (with or without hysterectomy) more than 6 weeks prior to enrollment
- The patient had a hysterectomy

Female patients of reproductive or childbearing potential who are unwilling to use a highly effective method of contraception for the duration of the study and for at least 18 weeks after the last dose of study treatment are excluded from study participation.

Examples of highly effective contraception include the following:

- Contraceptive pill or transdermal patch
- Single barrier plus spermicide
- Intrauterine device
- Implants for contraception
- Injections for contraception (with prolonged release)
- Hormonal vaginal device
- Sterilization, surgical tubal ligation
- Sole sexual partner consisting of surgically sterilized male partner with appropriate postsurgical verification of the absence of spermatozoa in the ejaculate

Patients may provide verbal confirmation that the partner completed appropriate follow-up after vasectomy. Sites are not required to obtain partner medical records.

Appendix 10

High-Resolution Computed Tomography Criteria for UIP Pattern

TABLE 4. HIGH-RESOLUTION COMPUTED TOMOGRAPHY CRITERIA FOR UIP PATTERN

UIP Pattern (All Four Features)	Possible UIP Pattern (All Three Features)	Inconsistent with UIP Pattern (Any of the Seven Features)
<ul style="list-style-type: none"> ● Subpleural, basal predominance ● Reticular abnormality ● Honeycombing with or without traction bronchiectasis ● Absence of features listed as inconsistent with UIP pattern (see third column) 	<ul style="list-style-type: none"> ● Subpleural, basal predominance ● Reticular abnormality ● Absence of features listed as inconsistent with UIP pattern (see third column) 	<ul style="list-style-type: none"> ● Upper or mid-lung predominance ● Peribronchovascular predominance ● Extensive ground glass abnormality (extent > reticular abnormality) ● Profuse micronodules (bilateral, predominantly upper lobes) ● Discrete cysts (multiple, bilateral, away from areas of honeycombing) ● Diffuse mosaic attenuation/air-trapping (bilateral, in three or more lobes) ● Consolidation in bronchopulmonary segment(s)/lobe(s)

Definition of abbreviation: UIP = usual interstitial pneumonia.

Appendix 11 Histopathological Criteria for UIP Pattern

TABLE 5. HISTOPATHOLOGICAL CRITERIA FOR UIP PATTERN

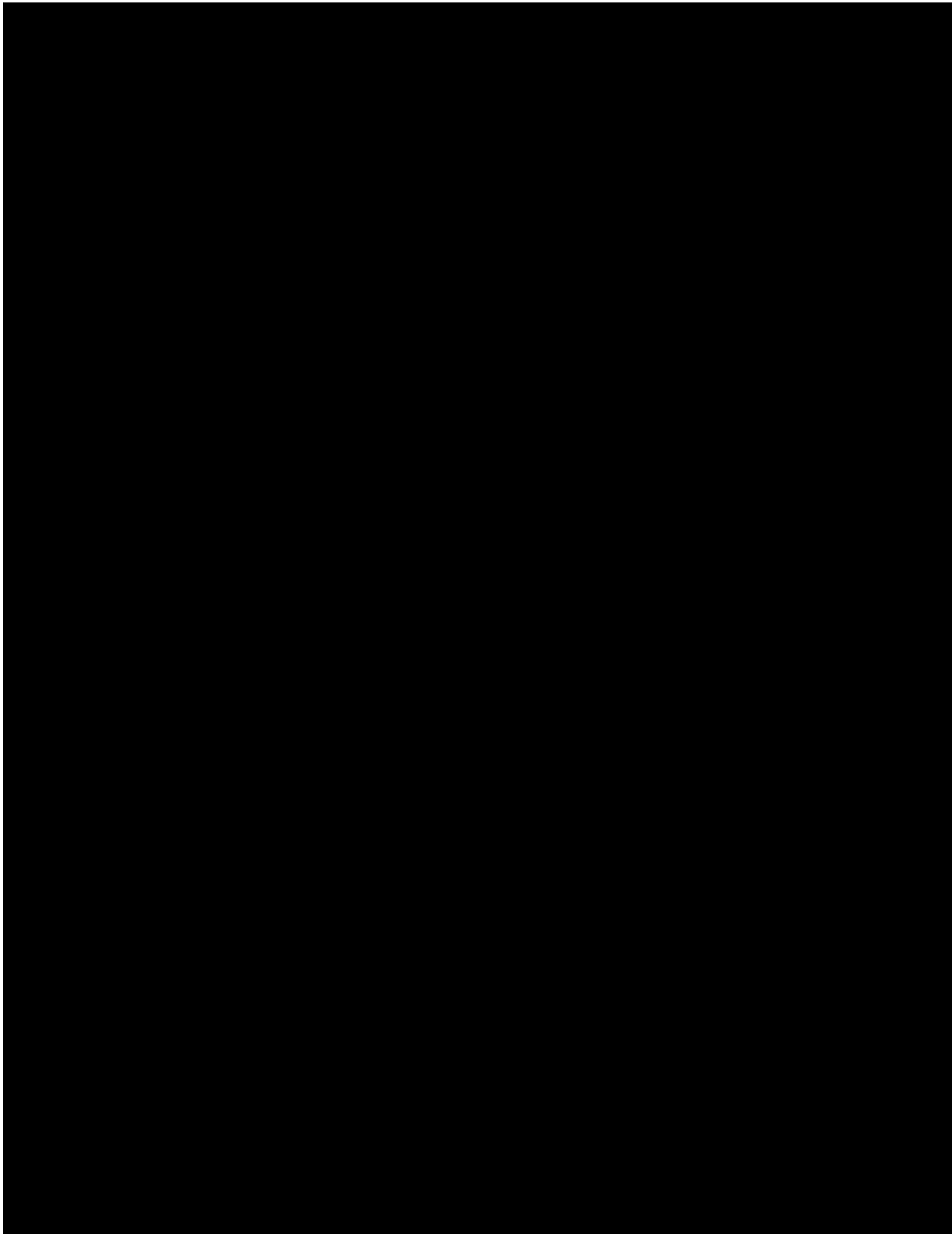
UIP Pattern (All Four Criteria)	Probable UIP Pattern	Possible UIP Pattern (All Three Criteria)	Not UIP Pattern (Any of the Six Criteria)
<ul style="list-style-type: none"> ● Evidence of marked fibrosis/ architectural distortion, ± honeycombing in a predominantly subpleural/ paraseptal distribution ● Presence of patchy involvement of lung parenchyma by fibrosis ● Presence of fibroblast foci ● Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column) 	<ul style="list-style-type: none"> ● Evidence of marked fibrosis / architectural distortion, ± honeycombing ● Absence of either patchy involvement or fibroblastic foci, but not both ● Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column) <li style="text-align: center;">OR ● Honeycomb changes only[‡] 	<ul style="list-style-type: none"> ● Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation ● Absence of other criteria for UIP (see UIP PATTERN column) ● Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column) 	<ul style="list-style-type: none"> ● Hyaline membranes* ● Organizing pneumonia[†] ● Granulomas[†] ● Marked interstitial inflammatory cell infiltrate away from honeycombing ● Predominant airway centered changes ● Other features suggestive of an alternate diagnosis

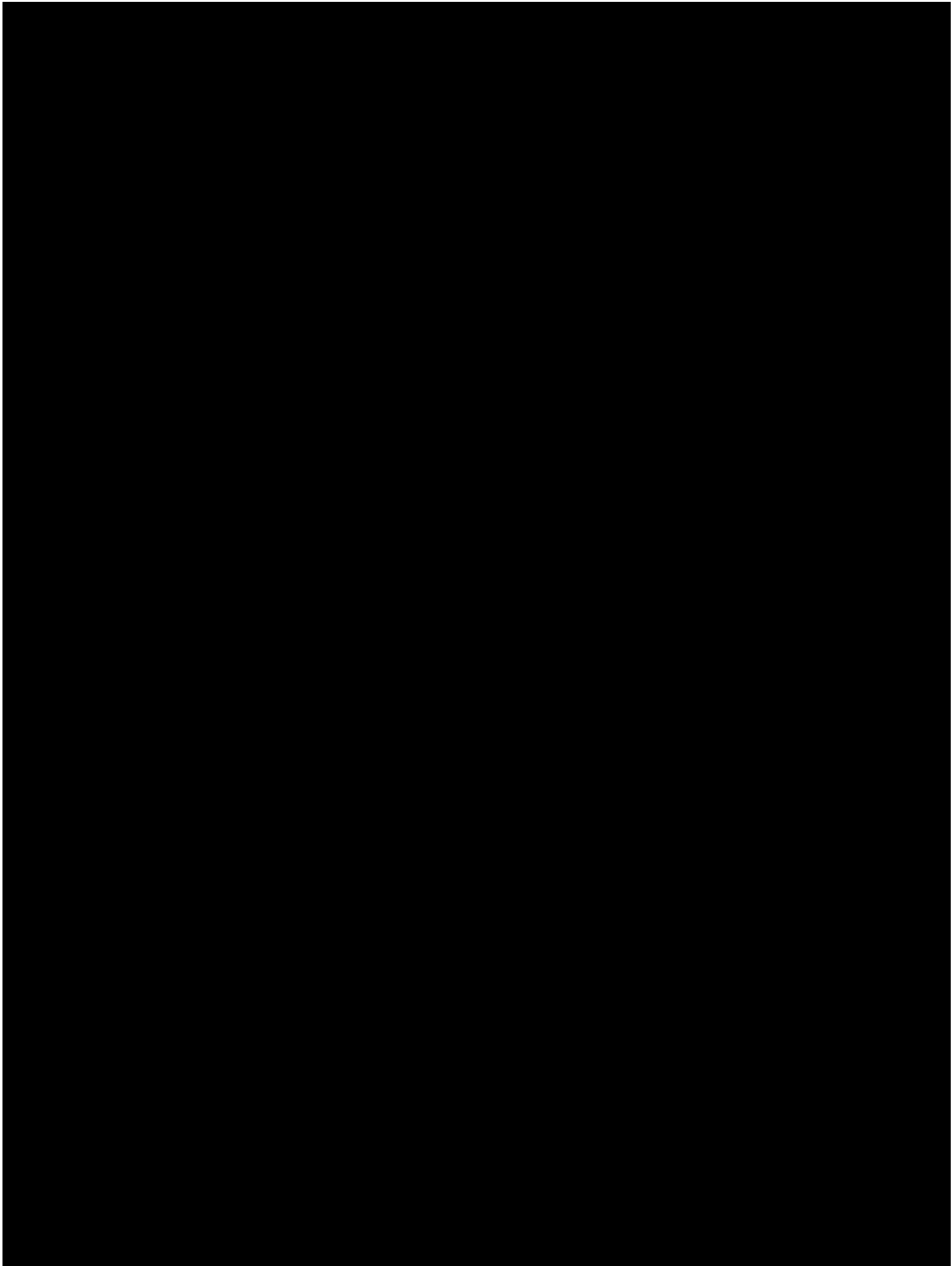
Definition of abbreviations: HRCT = high-resolution computed tomography; UIP = usual interstitial pneumonia.

* Can be associated with acute exacerbation of idiopathic pulmonary fibrosis.

[†] An isolated or occasional granuloma and/or a mild component of organizing pneumonia pattern may rarely be coexisting in lung biopsies with an otherwise UIP pattern.

[‡] This scenario usually represents end-stage fibrotic lung disease where honeycombed segments have been sampled but where a UIP pattern might be present in other areas. Such areas are usually represented by overt honeycombing on HRCT and can be avoided by pre-operative targeting of biopsy sites away from these areas using HRCT.





STATISTICAL ANALYSIS PLAN

TITLE: A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, STUDY TO ASSESS THE EFFICACY AND SAFETY OF LEBRIKIZUMAB IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS

PROTOCOL NUMBER: GB28547

STUDY DRUG: Lebrikizumab (RO5490255)

VERSION NUMBER: 2

IND NUMBER: 117,062

EUDRACT NUMBER: 2013-001163-24

SPONSOR: F. Hoffmann-La Roche Ltd.

PLAN PREPARED BY: [REDACTED], Ph.D.

DATE FINAL: Version 1:16 May 2016.

DATE AMENDED: Version 2: See electronic date stamp below

STATISTICAL ANALYSIS PLAN APPROVAL

Name	Reason for Signing	Date and Time (UTC)
[REDACTED]	Company Signatory	13-Sep-2017 12:21:00

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STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

The Statistical Analysis Plan GB28547 Version 2 was amended as follows:

- Respiratory hospitalization was added as a secondary endpoint due to a publication (Paterniti et al. 2017) that supports respiratory hospitalization is a clinically relevant endpoint and was a strong predictor of mortality in an analysis of pooled data from the placebo arms of the Esbriet and OFEV Phase III studies.
- The secondary endpoints hierarchy was reordered [REDACTED]
[REDACTED]
- Time from randomization to first occurrence of a $\geq 15\%$ absolute decrease in percentage of predicted DL_{CO} or death from any cause was added as an endpoint to parallel a similar analysis for FVC.
- An endpoint of annualized rate of decline in SpO₂ was added as an exploratory endpoint based on review of the Phase II OFEV study results and post hoc examination of GB28547 Cohort A results.
- The number of imputations for multiple imputation was changed from 1000 to 100 to reduce the computational burdens because it was realized that 100 is sufficient for estimation.
- Additional minor changes have been made to improve clarity and consistency.

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1. **BACKGROUND**

This statistical analysis plan (SAP) provides details on the study design, outcome measures, and statistical analysis plan for Study GB28547. The outcome measures and the statistical analysis plan in this SAP supersede those specified in the protocol. The SAP was finalized prior to Cohort A unblinding and is currently being amended prior to unblinding Cohort B.

[REDACTED] Since then, two agents have been approved for the treatment of idiopathic pulmonary fibrosis (IPF) (Esbriet[®] [pirfenidone], Ofev[®] [nintedanib]), and Study GB28547 has been re-designed to support registration and labeling. Key changes to study design since 2013 have included:

- Revision of primary endpoint from progression free survival (PFS) to annual rate of decrease in percentage of predicted forced vital capacity (FVC, reflected in this SAP)
- Addition of PFS as a key secondary endpoint
- Broadening of the eligibility criteria
- Addition of an independent Cohort B, to evaluate the effect of lebrikizumab in adjunct to/combination with pirfenidone background therapy compared with pirfenidone alone

After the analysis of Cohort A, the Sponsor formed an Internal Monitoring Committee (IMC) to perform an unplanned interim futility analysis of Cohort B to determine if the study should be terminated for lack of sufficient efficacy. Following this analysis, the decision was made to continue the study and not perform additional efficacy and/or futility interim analyses. The study continued to be monitored for safety by an external iDMC.

2. **STUDY DESIGN**

Study GB28547 is comprised of Cohort A and Cohort B. Each Cohort is a randomized, multicenter, double-blind, placebo-controlled, parallel-group study of lebrikizumab in patients with IPF. Cohort A patients were treated in the absence of pirfenidone IPF background therapy during the placebo controlled period of the study. Cohort B patients were treated with pirfenidone as background therapy. The two cohorts of patients are independent and enrolled sequentially: Cohort B enrollment initiated after the completion of enrollment in Cohort A on 8 April 2015. See Study Schemas in [Figure 1](#) and [Figure 2](#).

Cohort A (Monotherapy)

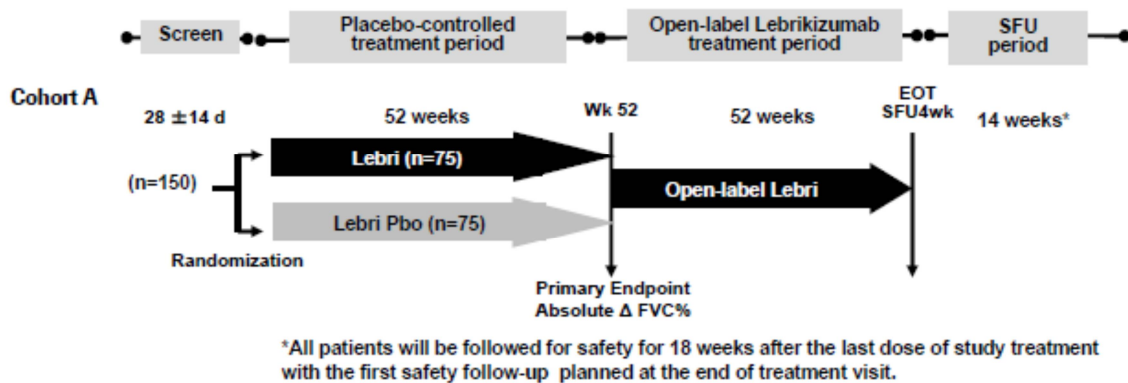
Approximately 150 patients were to be randomized 1:1 to lebrikizumab monotherapy at a dose of 250 mg or placebo every 4 weeks for a total of 52 weeks.

Patients who provided written informed consent would commence a screening period, which lasted approximately 28 days to establish entry criteria. Study treatment was administered by subcutaneous (SC) injection every 4 weeks, with the first injection occurring at the randomization visit (Day 1/Visit 2). Patients continued to receive blinded study treatment every 4 weeks during the placebo-controlled treatment period for a total of 13 doses/26 injections of blinded treatment.

Patients in Cohort A who had not prematurely discontinued study treatment could continue into the 52-week open-label lebrikizumab treatment period. All patients who continued into the 52-week open-label lebrikizumab treatment period would receive SC lebrikizumab at a dose of 250 mg every 4 weeks. All patients were followed for safety for 18 weeks after the last dose of study treatment.

See the protocol for details in eligibility criteria and study assessments.

Figure 1 Cohort A Study Schematic



d = day; EOT = end of treatment; FVC = forced vital capacity; Lebri = lebrikizumab; n = number of patients; PBO = placebo; SFU = safety follow-up; wk = week.

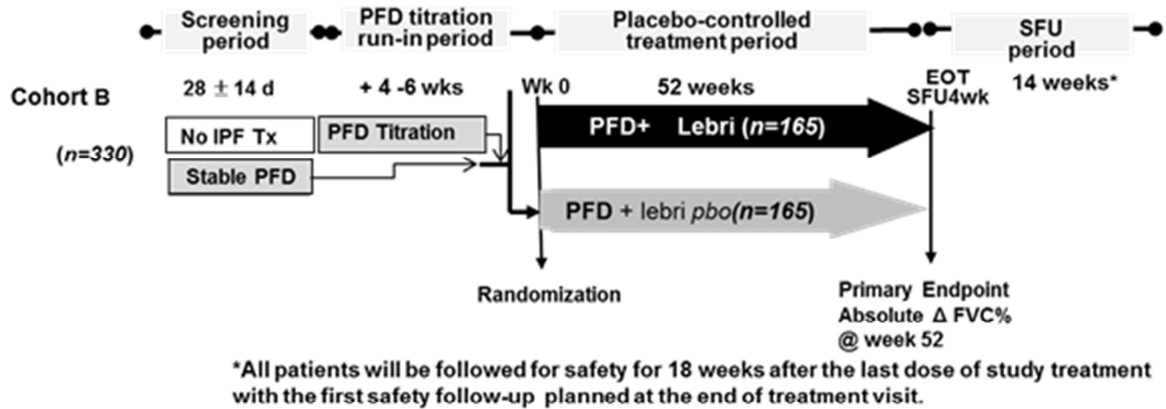
Cohort B (Combination Therapy)

Approximately 330 patients were to be randomized 1:1 to either lebrikizumab 250 mg or placebo every 4 weeks in combination with pirfenidone for a total of 52 weeks. Patients were to be treated daily with the maximum tolerated dose of pirfenidone ≤2403 mg/d.

Patients who provided written informed consent would commence a screening period, which would last approximately 28 days to establish entry criteria. Study treatment would be administered by SC injection every 4 weeks, with the first injection occurring at the randomization visit (Day 1/Visit 2). Patients would continue to receive blinded study treatment every 4 weeks during the placebo-controlled treatment period for a total of 13 doses (26 injections) of blinded treatment. All patients would be followed for safety for 18 weeks after the last dose of study treatment.

See the protocol for details in eligibility criteria and study assessments.

Figure 2 Cohort B Study Schematic



1

d=days; EOT=end of treatment; FVC=forced vital capacity; Lebri=lebrikizumab; n=number of patients; pbo=placebo; PFD=pirfenidone; SFU=safety follow-up; wks=weeks.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in [Appendix 1](#). For additional details, see the Schedule of Assessments in [Appendix 2](#), [Appendix 3](#), [Appendix 4](#), and [Appendix 5](#).

2.2 OUTCOME MEASURES

2.2.1 Primary Efficacy Outcome Measures

The primary efficacy outcome measure for this study is the annualized rate of decrease in percentage of predicted FVC over 52 weeks (% FVC/year). See protocol for description of spirometry.

2.2.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures of this study are as follows:

- Annualized rate of decrease in 6-Minute Walk Test (6MWT) distance over 52 weeks
- Time from randomization to first occurrence of a $\geq 10\%$ absolute decrease in percentage of predicted FVC or death from any cause
- Annualized rate of decrease in percentage of predicted diffusion capacity of the lung for carbon monoxide (DL_{CO}) over 52 weeks
- PFS, defined as the time from study treatment randomization to the first occurrence of any of the following disease progression or death events:

Death from any cause

All-cause hospitalization

A decrease from baseline (relative change) of $\geq 10\%$ in FVC (L)

- Annualized rate of decrease in FVC (mL/year) over 52 weeks
- Annualized rate of change in A Tool to Assess Quality of Life in IPF (ATAQ-IPF) total score over 52 weeks (see protocol for description of the instrument)
- Time from randomization to first occurrence of St. George's Respiratory Questionnaire (SGRQ; see protocol for description of the questionnaire) worsening (total score) as defined by reaching Minimal Important Difference (MID; [Swigris et al. 2010](#))

Total Score ≥ 7 or death from any cause

- Time from randomization to non-elective hospitalization or death from any cause
- Time from randomization to first event of acute IPF exacerbation (defined below)

IPF exacerbation is defined as an event that meets all of the following criteria as determined by the investigator:

Unexplained worsening or development of dyspnea within the previous 30 days

And radiologic evidence of new bilateral ground-glass abnormality or consolidation, superimposed on a reticular or honeycomb background pattern, that is consistent with UIP

And absence of alternative causes, such as left heart failure, pulmonary embolism, pulmonary infection (on the basis of endotracheal aspirate or bronchoalveolar lavage if available, or investigator judgment), or other events leading to acute lung injury (e.g., sepsis, aspiration, trauma, reperfusion pulmonary edema)

- Time from randomization to death from any cause
- Time from randomization to Respiratory hospitalization
- Time from randomization to first occurrence of a $\geq 15\%$ absolute decrease in percentage of predicted DL_{CO} or death from any cause

2.2.3 Exploratory Efficacy Outcome Measures

The exploratory outcome measures for this study are as follows:

- Change from baseline to Week 52 in radiographic findings on pulmonary high-resolution computed tomography (HRCT), including quantitative lung fibrosis (QLF) score (see protocol)
- Change from screening (corresponding to timing for randomization strata) in serum and plasma biomarkers (e.g., periostin and CCL18) and change from baseline in serum and plasma biomarkers (e.g., periostin, CCL18, YKL40, COMP, OPN, CCL13)
- Serum lebrikizumab concentrations during the extended treatment and the 14-week safety follow-up period
- Exposure-response relationships (to be evaluated as warranted)
- Change from baseline to Week 52 in the Borg CR10 Scale
- Change from baseline to Week 52 in the ATAQ-IPF

- Time from randomization to first occurrence of SGRQ individual domain worsening as defined by reaching MID ([Swigris et al. 2010](#)).
 - Symptom=8
 - Activity=5
 - Impact=7
 - or death from any cause
- Change from baseline to Week 52 in the SGRQ
- Annualized rate of decrease in oxygen saturation levels (SpO₂) (%) over 52 weeks

The analysis plan for the exploratory HRCT and biomarkers will be specified in a separate document.

2.2.4 Pharmacokinetic Efficacy Outcome Measures

The pharmacokinetic (PK) outcome measures for this study are as follows:

- Serum lebrikizumab concentration at Week 52 (C_{Wk52})
- Predose serum lebrikizumab concentrations (C_{min}) at Weeks 4, 12, 24, and 36 ($C_{min,Wk4}$, $C_{min,Wk12}$, $C_{min,Wk24}$, and $C_{min,Wk36}$)

2.2.5 Safety Outcome Measures

The safety outcome measures are the same as those specified in the Protocol Synopsis (see [Appendix 1](#)).

2.3 DETERMINATION OF SAMPLE SIZE

Cohort A

Approximately 150 patients were to be enrolled. A sample size of 75 patients in each treatment group would provide over 85% power to detect a mean change from baseline in percentage of predicted FVC at 52 weeks from 6.6% to 3.0% (a 3.6% absolute difference or 54% relative reduction) under the assumption that the common standard deviation is 7% (as reported in the placebo group in the PIPF-016 [ASCEND] trial of pirfenidone). Power was estimated with use of a two group t-test at a 0.05 two-sided significance level.

A sample size of 75 patients in each treatment group will provide approximately 80% power to detect a change in the annualized rate of decrease in percentage of predicted FVC over 52 weeks from 7.2% to 3.5% (a 3.7% absolute difference or 51% relative reduction) under the assumption that the common standard deviation is 8% (as reported in the placebo group in the ASCEND trial of pirfenidone). Power was estimated with use of a two group t-test at a 0.05 two-sided significance level.

Cohort B

Approximately 330 patients were to be enrolled. A sample size of 165 patients in each treatment group would provide over 85% power to detect a mean change from baseline

in percentage of predicted FVC at 52 weeks from 3.7% to 1.3% (a 2.4% absolute difference or 64% relative reduction) under the assumption that the common standard deviation is 7% (as reported in the pirfenidone group in the ASCEND trial of pirfenidone). Power was estimated with use of a two group t-test at a 0.05 two-sided significance level.

A sample size of 165 patients in each treatment group will provide approximately 80% power to detect a change in the annualized rate of decrease in percentage of predicted FVC over 52 weeks from 4.1% to 1.6% (a 2.5% absolute difference or 60% relative reduction) under the assumption that the common standard deviation is 8% (as reported in the pirfenidone group in the ASCEND trial of pirfenidone). Power was estimated with use of a two group t-test at a 0.05 two-sided significance level.

2.4 ANALYSIS TIMING

The primary analysis for Cohort A was performed after all patients enrolled in Cohort A had either completed the placebo-controlled treatment visit (Week 52) or discontinued early from the study. Treatment assignment was unblinded when all data through the Week 52 visit were in the database and the data were cleaned and verified. The independent Data Coordinating Center (iDCC) that prepares the safety analyses for independent Data Monitoring Committee (iDMC) review prepared the unblinding data of Cohort A for the Sponsor to ensure that the Cohort B was not inadvertently unblinded, when Cohort A was unblinded.

The primary analysis for Cohort B will be performed after all patients enrolled in Cohort B have either completed the placebo-controlled treatment visit (Week 52) or discontinued early from the study. Treatment assignment will be unblinded when all data through the Week 52 visit are in the database and the data have been cleaned and verified.

3. STUDY CONDUCT

3.1 RANDOMIZATION

Patients were randomized to the treatment arms through the interactive voice/Web-based response system (IxRS). After written informed consent is obtained, patients received a screening number, which was assigned by the IxRS. Following completion of the screening period and after all patient eligibility requirements were confirmed on Day 1, patients were to be assigned an identification number (a different number from the screening number) and randomized in a 1:1 ratio to one of two treatment arms for the 52-week placebo-controlled study period:

- **Cohort A** - lebrikizumab 250 mg SC or placebo SC every 4 weeks
- **Cohort B** - lebrikizumab 250 mg SC every 4 weeks and pirfenidone \leq 2403 mg/d or placebo SC every 4 weeks and pirfenidone \leq 2403 mg/d

Patients were to be randomized on the same day that treatment was to be initiated (Day 1/Visit 2).

Dynamic hierarchical randomization was performed centrally and stratified by the following factors:

- **Cohort A:** region (United States, Europe/Canada, other), lung function (FVC < 50%, 50% to 75%, > 75% predicted), and serum periostin concentration (< 50 ng/mL, ≥ 50 ng/mL)
- **Cohort B:** region (United States, Europe/Canada, other), lung function (FVC < 50%, 50% to 75%, > 75% predicted), and serum periostin concentration (< 50 ng/mL, ≥ 50 ng/mL). Although in the protocol amendment version 6 (2 December 2015) the region strata was to be replaced by prior perfenidone exposure but due to faster than anticipated accrual and logistic challenges this change was not implemented.

During the placebo-controlled study period and the open-label lebrikizumab treatment period, IxRS assigned study treatment kits for patients in Cohort A. During the placebo-controlled study period, IxRS will assign study treatment kits and pirfenidone treatment kits for patients in Cohort B. At each dosing visit during the placebo-controlled period, study and/or pirfenidone treatment kits will be distributed for administration. The placebo and active kits are filled and packaged to look identical. Patient randomization and treatment kit assignments will be verified on an ongoing basis by an external and independent statistical coordinating center to ensure that randomization and kit assignments are conducted correctly by IxRS.

The dynamic randomization scheme was employed with a biased-coin assignment whenever an imbalance at a given hierarchical level exceeds pre-specified thresholds. The dynamic randomization parameters (i.e., the allocation probabilities and the imbalance thresholds that lead to a biased-coin assignment at each level) will be provided in the Clinical Study Report (CSR).

Patients, all study site personnel, and the Sponsor and its agents (with the exception of the IxRS service provider, the external independent statistical coordinating center responsible for verifying patient randomization and study treatment kit assignments, PK/PD laboratory personnel, and the iDMC, iDCC, and IMC members) will be blinded to treatment assignment for each cohort until the unblinding for each primary analysis.

If unblinding is necessary for patient management (in the case of a serious adverse event [SAE]), the treatment code is available to the investigator through the IxRS. Treatment codes are not to be disclosed except in emergency situations. If the investigator wishes to know the study treatment assignment for any other reason, he or she is to contact the Medical Monitor directly. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding or unblinding because of a SAE).

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

3.2 INDEPENDENT REVIEW FACILITY

See protocol for details on planned independent reviews for HRCT, surgical lung biopsy, and ECG.

3.3 DATA MONITORING

3.3.1 Independent Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will monitor safety and study conduct on an ongoing basis. Members of the iDMC will be external to the Sponsor, and will follow a charter that outlines the iDMC roles and responsibilities. The iDMC will meet approximately every 6 months to review unblinded safety and study conduct data provided by an iDCC. This will include a review of all deaths and hospitalizations reported on the adverse event (AE) forms. The study may be stopped early for safety reasons. If the iDMC determines that a benefit-risk assessment is necessary, the iDMC may also review unblinded efficacy data, although the iDMC may not recommend stopping the trial for positive efficacy. Full details of the meeting schedule and flow of information between iDCC and iDMC can be found in the iDMC charter.

3.3.2 Independent Anaphylaxis Adjudication Committee

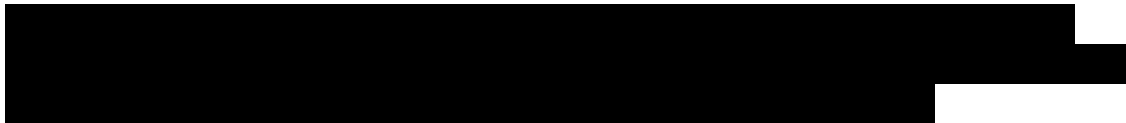
An independent Anaphylaxis Adjudication Committee (iAAC) reviews AEs or groups of AEs that are identified as potential cases of anaphylactic, anaphylactoid, or hypersensitivity reactions. Members of the iAAC are external to the Sponsor and review blinded data to adjudicate cases as anaphylaxis per Sampson's criteria (see [Appendix 7; Sampson et al. 2006](#)).

A detailed description of the procedures and data flow of the AAC is maintained in a separate AAC Charter.

3.3.3 Internal Monitoring Committee

[REDACTED]

[REDACTED]



Details with regard to the IMC were documented in an IMC agreement.

4. STATISTICAL METHODS

Cohort A and Cohort B are two independent studies under the same protocol; patients were enrolled with the same entry criteria. The effect of lebrikizumab in the treatment of IPF was assessed as a monotherapy in Cohort A and in combination with pirfenidone in Cohort B. Cohort B was initiated after the completion of the enrollment in Cohort A; Cohort A patients are not allowed to enter Cohort B. Analyses will be performed for each study separately.

The primary analysis will be performed after the completion of the 52-week randomized placebo-controlled period. Analyses will include all assessments up to Week 52.

Descriptive summaries will include mean, standard deviation, median and range for continuous variables, and counts and percentages for categorical variables.

All analyses will be performed using SAS software (Version 9.2 or higher).

4.1 ANALYSIS POPULATIONS

4.1.1 Intent-to-Treat Population

The intent-to-treat (ITT) population will be comprised of all patients who were randomized in the study. All efficacy analyses will be performed on this population with patients grouped according to the treatment assignment at randomization.

4.1.2 Per Protocol Population

A per-protocol population is not deemed necessary for this study and is not defined. However, ongoing monitoring throughout the study course will track the number of patients who violate protocol-defined eligibility or study conduct criteria.

4.1.3 Pharmacokinetic-Evaluable Population

The PK-evaluable population will include all patients who have received at least one dose of study drug, and have at least one non-missing PK observation. Data from these patients will be included in PK analyses, as appropriate, depending on the available time points.

4.1.4 Safety Population

Safety analyses will be based on all patients who received at least one dose of study drug, with patients grouped according to the actual treatment received.

4.2 ANALYSIS OF STUDY CONDUCT

For each cohort, the number of patients randomized will be tabulated by study site and treatment arm. Patient disposition (the number of patients treated and completing each study period) will be tabulated by treatment arm. Premature treatment discontinuation and study discontinuation, as well as reasons for discontinuations, will be summarized.

Eligibility criteria deviations and other major protocol deviations will be summarized.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics such as age, gender, race, ethnicity, measures of disease severity, comorbid illnesses, baseline pulmonary function (percentage of predicted FVC and DL_{CO}) and screening biomarker levels (periostin and CXCL13) will be summarized for all randomized patients by treatment arm with use of descriptive statistics. Continuous variables will be summarized with the number, mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized with patient counts and percentages. Baseline data will be defined as the last observation before randomization.

4.4 EFFICACY ANALYSIS

All efficacy analyses will be performed on the Randomized Population. Unless otherwise specified, data collected during the 52-week placebo-controlled period will be used, regardless of whether the patient remained on treatment or discontinued the study drug early (but remained in the study). Analyses will be performed for Cohort A and Cohort B separately. For hypothesis testing, each cohort will be considered as a separate study and no type I error control will be done across the two cohorts.

For change-from-baseline endpoints, the baseline value will be defined as the measurement at randomization (Visit 2). If the randomization value is not available, the screening (Visit 1) value can be used in its place (last measurement prior to Day 1). For each subject, relative and absolute changes from baseline will be defined as follows:

- Absolute change from baseline = (post-baseline value – baseline value)
- Relative (%) change from baseline = $100 * (\text{post-baseline value} - \text{baseline value}) / (\text{baseline value})$

4.4.1 Type I Error Control Plan

The fixed-sequence testing procedure ([Westfall and Krishen, 2001](#)) will be used to control the overall type I error rate for statistical testing of the primary and key secondary efficacy endpoints.

Contingent upon statistical significance in the primary efficacy endpoint—annualized rate of decrease in percentage of predicted FVC over 52 weeks, the key secondary endpoints will be tested at a two-sided significance level of 5% in the order as shown below:

- Time from randomization to death from any cause
- Annualized rate of decrease in percentage of predicted DL_{CO} over 52 weeks
- Time from randomization to first respiratory-related hospitalization
- Time from randomization to first acute exacerbation or death from any cause
- Annualized rate of change in the ATAQ-IPF total score over 52 weeks
- Annualized rate of decrease in 6MWT distance over 52 weeks
- Time from randomization to first occurrence of a $\geq 15\%$ absolute decrease in percentage of predicted DL_{CO} or death from any cause
- Time from randomization to first occurrence of a $\geq 10\%$ absolute decrease in percentage of predicted FVC or death from any cause
- PFS defined as time to all-cause death, all-cause hospitalization or $\geq 10\%$ relative decrease in FVC (L), whichever occurs first

If a test is not significant at 0.05 level, then the subsequent test(s) will not be considered significant regardless of the associated p-value(s).

4.4.2 Primary Efficacy Endpoint

The primary endpoint is annualized rate of decrease in percentage of predicted FVC through Week 52, which will be compared across treatment arms with use of a random slope model on observed cases at a 0.05 two-sided significance level.

The statistical model is as follows:

$$FVC_{ijk} = (\beta_0 + \beta_{0k}) + (\alpha_i * \beta_1 + \beta_{1k}) * t_k + \eta_k + \epsilon_{ijk}$$

where FVC_{ijk} is the predicted FVC for kth patient at visit j in treatment group i; β_0 is the intercept; α_i and β_1 is the interaction term of the treatment effect ($i = \text{lebri or placebo}$) and the slope; t_k is assessment time (continuous in year) for patient k; η_k is the effect of baseline lung function (defined as $FVC < 50\%$ vs. 50% to 75% vs. $> 75\%$ predicted) for the kth patient; β_{0k} and β_{1k} are the random components for intercept and slope; ϵ_{ijk} is the random error for kth patient at time j; β_{0k} , β_{1k} , and ϵ_{ijk} are assumed to be independent and normally distributed with mean 0 and variance of σ_0^2 , σ_1^2 , and σ_ϵ^2 respectively.

Of note, because of a relatively large number of strata defined by the randomization stratification factors, the analysis will be adjusted for baseline lung function only because baseline FVC may impact the clinical disease course.

From the model, least squares means for the annualized rate of decrease in each treatment arm and the difference between the two treatment arms will be provided with

95% CIs. The model implicitly imputes missing data based on an individual's estimated rate of worsening of lung function prior to study visit discontinuation (i.e., assuming missing at random).

There are several different approaches to summarizing the treatment effect which are ways of understanding the results rather than independent endpoints. For summarizing treatment effect the following will be provided but not considered as separate endpoints or hypotheses.

- Change from baseline to landmark visit time expressed as absolute and relative difference
- Difference in annual rate of decrease expressed as absolute and relative difference
- Categorical absolute change from baseline to each visit time with categories of decrease of $\geq 10\%$ or death before the visit, decrease of 10% to $>0\%$, stability or improvement of change $\geq 0\%$

Change from baseline in percentage of predicted FVC at Week 52 will be analyzed as a sensitivity analysis with use of a mixed-effects model for repeated measures (MMRM) on observed cases at a 0.05 two-sided significance level.

The statistical model is as follows:

$$\text{Chg}_{ijk} = \beta_0 + \alpha_i * \beta_j + \eta_k + \varepsilon_{ijk}$$

where Chg_{ijk} is the change in percentage of predicted FVC for k th patient at visit j in treatment group i ; β_0 is the intercept; $\alpha_i * \beta_j$ is the interaction term of the treatment and categorical visit effect ($i = \text{lebri or placebo}$, $j = \text{Weeks 1, 4, 12, 24, 36, 44, and 52}$; $\alpha_{\text{placebo}} * \beta_{12} = 0$); η_k is the effect of baseline lung function (defined as $\text{FVC} < 50\%$ vs. 50% to 75% vs. $> 75\%$ predicted) for the k th patient; ε_{ijk} is the random error for k th patient at time j and is assumed to be independent and normally distributed with mean 0 and unstructured variance-covariance V . If this analysis fails to converge, analyses using compound symmetry or first order autoregressive structures as alternatives will be investigated.

From the model, least squares means for the absolute change from baseline as well as placebo corrected absolute changes with 95% CIs for each treatment arm at each post-baseline visit will be estimated.

Other sensitivity analyses using various imputation/analysis strategies will also be performed. See Section 4.4.5 for details.

4.4.3 Secondary Efficacy Endpoints

Time-to-Event Endpoints

The log rank test stratified by baseline lung function ($\text{FVC} < 50\%$ vs. 50% to 75% vs. $> 75\%$ predicted) will be used to compare the time to event endpoints between two treatment arms. The hazard ratio and its 95% CI will be estimated using a Cox regression model

stratified by baseline lung function. In fitting the Cox model, ties will be handled with the approximate likelihood method of Efron (1977). Kaplan-Meier plots will be provided.

Time-to-event will be measured in reference to the date of randomization. The primary efficacy assessments for the randomized placebo-controlled period are made on through the Week 52 visit, assessment on this day will be included for analyses of the randomized placebo-controlled period, but subsequent assessment during the open-label period or after Week 52 will be excluded. Patients are considered to be in the placebo controlled period even if they have discontinued study treatment if they would still be receiving placebo controlled study treatment had they not discontinued. For time to non-elective hospitalization or death from any cause, time to first event of acute IPF exacerbation, time from randomization to death from any cause, and time to respiratory hospitalization, patients not experiencing an event will be censored at the earlier of last known alive day, study day 368 or the last date during the placebo-controlled period.

For time to first occurrence of a $\geq 10\%$ absolute decrease in percentage of predicted FVC or death from any cause, time to PFS, time to first occurrence of a $\geq 15\%$ decrease in percentage of predicted DL_{CO} or death from any cause, and time to first SGRQ Total Score ≥ 7 or death from any cause, deaths which occur within 168 days after the last clinic assessment and before the week 52 visit (and before start of open label treatment) will be counted as events. For the PFS analysis, hospitalization will be counted as events following the same rule as for death. Patients without an event will be censored at the last clinic assessment during the placebo controlled period. Any patients who undergo lung transplantation will be censored at the date of the transplant. Sensitivity analyses will be provided with lung transplant counted as an event for PFS and time from randomization to death or non-elective hospitalization from any cause. For the sensitivity analyses, only lung transplant, death, or non-elective hospitalization which occur within 168 days after the last clinic assessment and before the week 52 visit (and before start of open label treatment) will be counted as events.

Annualized Rate of Decrease Endpoints

The annualized rate of decrease in FVC (mL/year) will be analyzed and summarized with use of the same method as for the annualized rate of decrease in percentage of predicted FVC. Diffusing capacity, 6MWT distance, and the ATAQ-IPF score will also be analyzed and summarized with the same methods. For the annualized rate of decrease in FVC (mL/year) height, sex, and age will be included in the model as covariates.

Categorical summaries will be provided with categories of decrease of ≥ 50 meters or death before the visit, decrease of 50 to >0 meters, and stability or improvement of ≥ 0 meters for the 6MWT distance; summaries will be provided with categories of decrease of $> 15\%$ or death before visit, decrease of 15% to $>0\%$, stability or improvement of $\geq 0\%$ for percentage of predicted DL_{CO}.

Rules for missing ATAQ-IPF V3 and SGRQ data are described in Section 4.8.

4.4.4 Exploratory Efficacy Endpoints

Time-to-Event Endpoints

These endpoints will be analyzed and summarized with use of the same methods for the time-to-event secondary endpoints.

Change-from-Baseline Endpoints

These endpoints will be analyzed and summarized with use of the same methods as the endpoint—change from baseline in percentage of predicted FVC in Section 4.4.2.

Annualized Rate of Decrease Endpoints

The annualized rate of decrease in SpO₂ (%) over 52 weeks will be analyzed and summarized with use of the same method as for the annualized rate of decrease in percentage of predicted FVC.

4.4.5 Sensitivity Analyses

The following additional sensitivity analyses will be performed:

- A. A Rank ANCOVA analysis of change from baseline to week 52 in percentage of predicted FVC stratified by baseline lung function (FVC < 50% vs. 50% to 75% vs. > 75% predicted) will be performed with death ranked as worst according to time until death (patient with the shortest survival time will be assigned the worst rank) and other missing results imputed the last observation carried forward method. These analyses will be performed as described in [Stokes et al. 2000](#).
- B. The annualized rate of decrease in *percentage of* predicted FVC over 52 weeks and the annualized rate of decrease in percentage of predicted DL_{CO} over 52 weeks will be performed using the random slope model with missing due to death imputed with the worst value observed in the study during the randomized treatment period, through week 52, among any Cohort A patient. Other missing data will be implicitly imputed by the model based on an individual's estimated rate of worsening of lung function prior to study visit discontinuation (i.e., assuming missing at random).
- C. The annualized rate of *decrease in percentage of* predicted FVC over 52 weeks will be performed using the random slope model with missing data imputed with the multiple imputation method only from placebo patients. The multiple imputation method will be implemented with the following specifications.
 1. 100 imputation datasets will be created separately from steps a and b
 - a) The MCMC method will be used for partial imputation of non-monotone missingness, only to produce a monotone missing pattern. The seed will be 5815733.
 - b) The monotone method will then be used with regression method. The baseline lung function (FVC < 50% vs. 50% to 75% vs. > 75% predicted), treatment group, and all prior visits will be included in the model to impute the following visit. The seed will be 8246205

2. The random slope analysis will be performed for each imputation dataset and the results will be combined following the methodology developed by Rubin (1978, 1987).
- D. The absolute change from baseline to Week 52 in percent (%) predicted FVC and the absolute change from baseline to Week 52 in percentage of predicted DL_{CO} will be performed using the MMRM model with missing due to death imputed with the worst value observed in the study during the randomized treatment period, through Week 52, among any Cohort A patient. Other missing data will be implicitly imputed by the model (i.e. assuming missing at random).

4.4.6 Subgroup Analyses

Subgroup analyses will be performed to assess the impact of select baseline characteristics (see [Table 1](#)) on the change from baseline in percentage of FVC at 52 weeks, by examining the interaction with the study drug with use of the MMRM model. Each baseline factor will be analyzed separately. Some categories may be grouped to allow sufficient sample size for interpretation.

Table 1 Subpopulation Definitions

Baseline Characteristics	Categories
Geographic region	U.S. ROW
Age at randomization	< 65 years ≥ 65 to < 75 years ≥ 75 years
Sex	Female Male
Race/ethnicity	White Nonwhite
Time from IPF diagnosis to randomization	< 1 year ≥ 1 year
Baseline %FVC	< 55% predicted 55% to < 75% predicted ≥ 75% predicted
FEV ₁ /FVC	< 0.80 ≥ 0.80
Hgb-corrected DL _{CO} (% predicted) ^a	< 35% 35% to < 50% ≥ 50%
GAP Index (see Appendix 6)	I/II or III
Extent of fibrosis on HRCT at baseline, expressed as a QLF score	Divided at the median for initial summary score
Periostin	< 50 ng/mL ≥ 50 ng/mL
Duration of prior pirfenidone exposure (for Cohort B only)	0 (started after informed consent) < 1 year ≥ 1 year

FEV₁=forced expiratory volume in 1 second; FVC=forced vital capacity;
HRCT=high-resolution computed tomography; QLF=quantitative lung fibrosis; ROW=rest of world.

Note: Hispanic/Latino ethnicity grouped with nonwhite for subgroup analyses.

4.5 PHARMACOKINETIC ANALYSES

Individual and mean serum lebrikizumab concentration-versus-time data will be reported. During the treatment period, mean concentrations will be reported at Weeks 1, 4, 12, 24, 36, and 52 ($C_{\min,Wk1}$, $C_{\min,Wk4}$, $C_{\min,Wk12}$, $C_{\min,Wk24}$, $C_{\min,Wk36}$, C_{Wk52} , respectively). Estimates for these parameters will be tabulated and summarized (mean, standard deviation, coefficient of variation, median, minimum, and maximum). Additional PK analyses during the treatment period or the 18-week safety follow-up period may be conducted as appropriate. Population PK modeling may be performed to characterize inter-individual variability, which may be reported separately from the CSR.

Pharmacokinetic analysis will use actual times, if available. If actual times are missing, nominal times may be used or data with missing collection times may be excluded.

4.6 BIOMARKER ANALYSES

4.6.1 Pharmacodynamic Biomarker Analyses

The pharmacodynamic (PD) effect of lebrikizumab in IPF will be explored by measuring the levels of biomarkers, focusing on serum levels of chemokines (chemokine ligand [CCL]13, CCL17, and CCL18), and periostin. Other biomarkers of interest may be explored depending on data availability. All PD analyses will be conducted on the ITT population.

Pharmacodynamic marker measurements over time will be summarized graphically and will include median measurements, median absolute changes from baseline, and median percent changes from baseline by treatment group.

4.7 SAFETY ANALYSES

Safety analyses will be based on all patients who received at least one dose of randomized study drug, with patients grouped according to the actual treatment received. Safety summaries will be presented by treatment arm for all treated patients. In addition, safety listings will be provided for any events reported during pirfenidone exposure following informed consent on this study but prior to randomization.

Safety will be assessed through the summary of AEs, laboratory test results (including antibodies to lebrikizumab), ECG, and vital signs. These summaries will be produced separately for each cohort for the treatment period (placebo-controlled study treatment period including safety follow-up period for Cohort B patients or Cohort A patients not entering open label extension period and Cohort A open-label lebrikizumab period including the subsequent safety follow-up period).

4.7.1 Exposure of Study Drug

Exposure of study drug (lebrikizumab or placebo) will be summarized descriptively (mean, standard deviation, median, and range) for the following measures:

- Treatment duration [days]=(date of last administration – date of first administration + 1), where the date of first administration is the Visit 2 date
- Number of doses=total number of non-zero doses

4.7.2 Adverse Events

Verbatim descriptions of treatment-emergent adverse events (TEAEs) will be coded with use of the latest version of Medical Dictionary for Regulatory Activities (MedDRA) dictionary, and their incidence summarized for each treatment arm by system organ class (SOC) and preferred term. A TEAE is defined as any new AE reported, or any worsening of an existing condition reported on or after the first dose of study drug. In addition, separate summaries will be provided for TESAEs, deaths, and AEs leading to discontinuation of study drug.

Analyses will be performed by treatment group for events of special interest that include anaphylactic reactions, local injection-site reactions, infections, and malignancies.

- Anaphylactic reactions will be reviewed and adjudicated by the iACC.
- Local injection-site reactions will be identified with use of the MedDRA high-level term of “injection site reaction”.
- Infections, as identified with use of the MedDRA SOC of “infections and infestations”.
- Malignancies, as identified on the basis of the Standardized MedDRA Queries (SMQ) of “Malignancy”.

4.7.3 Laboratory Data

Serum chemistry and hematology, evaluations will be summarized by descriptive statistics for each treatment group, together with changes from baseline (Visit 2 value). In addition, all chemistry, hematology, urinalysis, and coagulation data outside the normal reference ranges will be tabulated in terms of the number and proportion of patients with values that are out of range. The toxicity grade at baseline and the highest toxicity grade during the placebo-controlled treatment phase for select labs (eosinophils absolute count, hemoglobin, WBC, platelets, alanine aminotransferase, aspartate aminotransferase, bilirubin, creatine kinase) will be summarized by treatment group.

The number and percentage of patients with positive serum antibodies at baseline and during the study will be tabulated.

4.7.4 Vital Signs

Vital signs data including temperature, systolic and diastolic blood pressure, pulse, and respiratory rate together with changes from baseline (Visit 2, pre-dose value) in these parameters will be summarized by treatment arm.

4.7.5 ECG Results

Descriptive summaries of ECG findings at baseline and throughout the study will be generated. The number and percentage of patients with abnormal ECG findings at baseline or new on-treatment ECG changes (e.g., QTc prolongation, presence of U waves) will be summarized.

4.8 MISSING DATA

Missing data will be handled as specified in the analysis method Section 4.4.

Missing individual items for the scoring of the SGRQ will be handled as follows: The symptoms component will be considered missing if more than two of the items are missing. The activity component will be considered missing if more than four of the items are missing. The impacts component will be considered missing if more than six of the items are missing. The total score will be considered missing if any component is missing. For a valid component questionnaire with unanswered questions, the predefined weight and score for a particular missing question will be used to calculate the aggregated score for the component (St George's Respiratory Questionnaire Manual, Version 2.3). Missing data will not be imputed.

Missing individual items for the scoring of the ATAQ-IPF will be handled as follows. If more than half of the items in a domain have responses, then scores for missing items may be imputed using the mean score from non-missing items. If half or more items are missing, then the domain is not scored.

4.9 INTERIM ANALYSES

It was not planned to conduct interim efficacy analyses. However, after the analysis of Cohort A, the Sponsor formed an IMC to perform an unplanned interim futility analysis of Cohort B to determine if the study should be terminated for lack of sufficient efficacy. Following this analysis, the decision was made to continue the study and not perform additional efficacy and/or futility interim analyses.

5. REFERENCES

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Appendix 1

Protocol Synopsis

TITLE: A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, STUDY TO ASSESS THE EFFICACY AND SAFETY OF LEBRIKIZUMAB IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS

PROTOCOL NUMBER: GB28547

VERSION NUMBER: 7

EUDRACT NUMBER: 2013-001163-24

IND NUMBER: 117,062

TEST PRODUCT: Lebrikizumab (RO5490255)

PHASE: II

INDICATION: Idiopathic Pulmonary Fibrosis

SPONSOR: F. Hoffmann-La Roche Ltd

Objectives

Efficacy Objectives

The primary efficacy objective for this study is to evaluate lebrikizumab compared with placebo as monotherapy or as combination therapy with pirfenidone background compared with placebo in patients with idiopathic pulmonary fibrosis (IPF), as measured by the *annualized rate of decline* in percentage of predicted forced vital capacity (FVC) *over 52 weeks*.

The secondary efficacy objectives are to evaluate lebrikizumab compared with placebo as monotherapy or as combination therapy with pirfenidone background therapy compared with placebo in patients with IPF as measured by:

- The efficacy on the basis of Progression Free Survival (PFS), pulmonary function, diffusion capacity, non-elective hospitalization for any cause, acute IPF exacerbation, *proportion of patients with at least 10% decline in percentage of predicted FVC or death, and all cause of death*
- The distance walked in 6 minutes and health-related quality of life questionnaires

Safety Objectives

The safety objectives for this study are the following:

- To evaluate the safety of lebrikizumab as monotherapy compared with placebo in patients with IPF
- To evaluate the safety of lebrikizumab with pirfenidone as background therapy compared with placebo with pirfenidone as background therapy in patients with IPF

Pharmacokinetic Objective

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

- To characterize the PK of lebrikizumab in patients with IPF

Appendix 1

Protocol Synopsis (cont.)

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To evaluate the efficacy of lebrikizumab compared with placebo as monotherapy or as combination therapy with pirfenidone compared with placebo in patients with IPF on the basis of changes in quantitative lung fibrosis (QLF) score on HRCT, *A Tool to Assess Quality of Life in IPF (ATAQ)*, and the BORG Category Ratio 10 Scale[®] (BORG CR10), and *time to first occurrence of St. George's Respiratory Questionnaire (SGRQ) individual domain worsening as defined by reaching minimal important difference (MID)*.
- To evaluate potential prognostic and predictive serum and whole blood RNA and DNA biomarkers associated with IPF

Study Design

Description of Study

This is a randomized, multicenter, double-blind, placebo-controlled, parallel-group study of lebrikizumab in patients with IPF. Approximately 480 patients with a diagnosis of IPF will be enrolled in the study across two cohorts (approximately 150 patients in Cohort A having approximately 75 patients per treatment arm and approximately 330 patients in Cohort B having approximately 165 patients per treatment arm) at approximately 120 sites located globally. The total treatment duration will be based on all patients receiving at least 13 doses (one dose every 4 weeks [Q4W]) of blinded treatment over 48 weeks. The study primary endpoint will measure the absolute change from baseline to Week 52 in percent predicted FVC.

Two cohorts of patients will be enrolled in the study; Cohort A patients will be treated in the absence of pirfenidone IPF background therapy; Cohort B patients will be treated with pirfenidone as background therapy.

Number of Patients

Approximately 480 patients with a diagnosis of IPF will be enrolled in the study across two cohorts (approximately 150 patients in Cohort A having approximately 75 patients per treatment arm and approximately 330 patients in Cohort B having approximately 165 patients per treatment arm) at approximately 120 sites located globally.

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 years at Visit 1
- Have a diagnosis of IPF based on the ATS/ERS/JRS/ALAT consensus statement on IPF within the previous 5 years from time of screening and confirmed at baseline.
- Have a central review assessment of an HRCT performed during the screening period or within 12 months prior to the start of screening.

All patients who have undergone a SLB as part of their initial workup should have pathology slides sent in for SLB central review assessment.

Eligibility will be determined on the basis of assessments in Table 1.

- A Multidisciplinary Discussion of Diagnosis (MDD) based on 2011 ATS/ERS/JRS/ALAT guidelines will be utilized to finalize the diagnosis in the event the initial central review outcome results for HRCT and SLB are disparate (inconsistent with UIP/definite UIP).

Additionally, patients must meet the following criteria for study entry:

- FVC $\geq 40\%$ and $\leq 100\%$ of predicted at screening

Appendix 1 Protocol Synopsis (cont.)

- Stable baseline lung function as evidenced by a difference of < 10% in FVC (L) measurements between screening and Day 1, Visit 2 prior to randomization
- Diffusion capacity of the lung for carbon monoxide (DL_{CO}) ≥ 25% and ≤ 90% of predicted at screening
- Ability to walk ≥ 100 meters unassisted in 6 minutes
- Cohort A: No background IPF therapy for ≥ 4 weeks allowed prior to randomization and throughout the placebo-controlled study period
- Cohort B: Tolerated dose of pirfenidone ≤ 2403 mg/QD for ≥ 4 weeks required prior to randomization and throughout the placebo-controlled study 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
- Evidence of other known causes of interstitial lung disease (ILD) (e.g., domestic and occupational environmental exposures, connective-tissue disease (CTD), and drug toxicity)
- Lung transplant expected within 12 months of screening
- Evidence of clinically significant lung disease other than IPF (e.g., asthma or chronic obstructive pulmonary disease [COPD])
- Post-bronchodilator forced expiratory volume in 1 second (FEV₁)/FVC ratio < 0.7 at screening
- Positive bronchodilator response evidenced by an increase of ≥ 12% predicted and 200 mL increase in either FEV₁ or FVC
- Any clinically significant medical disease (other than IPF) that is associated with an expected survival of < 12 months, likely to require a change in therapy during the study, or likely to impact the ability of the patient to participate in the study in the opinion of the investigator, or impact the study efficacy or safety assessments
- Requirement for continuous medical care and assistance, or limited ability to self-care that would impact the ability of patient to participate in the study or to perform the study-related assessments
- Class IV New York Heart Association chronic heart failure or historical evidence of left ventricular ejection fraction < 35%
- Hospitalization due to an exacerbation of IPF within 4 weeks prior to or during screening
- Known current malignancy or current evaluation for a potential malignancy
- Major episode of infection requiring any of the following:
 - Admission to the hospital for ≥ 24 hours within 4 weeks prior to screening or during screening and run-in period
 - Treatment with antibiotics (IV, IM, oral, or inhaled) within 4 weeks prior to screening or during screening and run-in period
- An active upper or lower respiratory tract infection occurring at any time within the screening period prior to the randomization visit (Visit 1 to Day 1, Visit 2)
- *Listeria monocytogenes* infection or active parasitic infection within 6 months prior to Day 1, Visit 2
- Active tuberculosis requiring treatment within 12 months prior to screening
- Known immunodeficiency, including but not limited to HIV infection

Appendix 1 Protocol Synopsis (cont.)

- Past 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
- 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 during screening
- Clinically significant abnormality on ECG at screening 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
- Receipt of a live/attenuated vaccine within the 4 weeks prior to Visit 1
- Chronic treatment with any of the following within 4 weeks or five half-lives prior to screening (whichever is longer) to the end of the placebo-controlled period (Day 365, Visit 16):
 - Immunosuppressive or immunomodulatory therapies (e.g., azathioprine, cyclosporine A, cyclophosphamide, D-penicillamine, interferon-gamma, tumor necrosis factor- α antagonists)
 - Cytotoxic drugs (e.g., colchicine) if used for IPF indication
 - Pirfenidone (Exclusion Limited to Cohort A)
 - N-acetylcysteine
 - Pulmonary hypertension therapies (e.g., endothelin receptor antagonist, phosphodiesterase type-5 inhibitor, riociguat, prostacyclin or prostacyclin analogue)
 - Tyrosine kinase inhibitors including exclusion of nintedanib for Cohort A and Cohort B
 - Warfarin or other anticoagulant therapy if given for IPF indication
 - Any unlicensed therapy given for IPF indication
 - Any investigational agent
- Chronic oral corticosteroid therapy is not permitted within 4 weeks prior to screening (Visit 1), during screening and run-in, *or throughout the study period*.
- History of alcohol, drug, or chemical abuse that would impair or risk the patient's full participation in the study, in the opinion of the investigator
- Female patients of reproductive potential who are not willing to use a highly effective method of contraception (e.g., contraceptive pill or transdermal patch, spermicide and barrier [i.e., condoms], intrauterine device, implants for contraception, injections for contraception [with prolonged release], hormonal vaginal device, sterilization, surgical tubal ligation) for the duration of the study and for at least 18 weeks after the last dose of lebrikizumab or placebo study treatment.
- Pregnant or lactating
- Body weight <40 kg

Additional exclusions that are limited to Cohort B (Pirfenidone Background):

- Known achalasia, esophageal stricture, or esophageal dysfunction sufficient to limit the ability to swallow oral medication
- Tobacco smoking or use of tobacco-related products within 3 months of screening or unwillingness to avoid smoking throughout the study (e.g., cigarette, pipe, cigar)
- Any condition that, as assessed by the investigator, might be significantly exacerbated by the known side effects associated with pirfenidone
- Known or suspected peptic ulcer

Appendix 1 Protocol Synopsis (cont.)

- Creatinine clearance < 40 mL/min, calculated using the Cockcroft-Gault formula
- Ongoing use or following therapies within 4 weeks of randomization (Day 1, Visit 2) or during the study
 - Strong inhibitors of CYP1A2 (e.g., fluvoxamine or enoxacin)
 - Moderate inducers of CYP1A2, limited to tobacco smoking and tobacco-related products

Length of Study

The total length of the study will be approximately 4 years from first patient screened to completion of the last patient visit. Individual patients may participate in the study for up to 2.9 years.

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 118 weeks after the last patient is enrolled and randomized into Cohort A. This timeframe includes a 52-week placebo-controlled period and a maximum of an additional 52 week open-label Lebrikizumab treatment period followed by the safety follow-up period. In the case that enrollment in Cohort B is slower than anticipated, LPLV is expected occur a maximum of 66 weeks after the last patient is enrolled and randomized into Cohort B. This timeframe includes a 52-weeks placebo-controlled period followed by the safety follow-up period. All patients will be followed for safety for 18 weeks after the last dose of study treatment of lebrikizumab or placebo by subcutaneous injection.

Outcome Measures

Efficacy Outcome Measures

The primary efficacy outcome measure for this study is the *annualized rate of decrease in percentage of predicted FVC over 52 weeks (% FVC/year)*.

Secondary Outcome Measures

The secondary efficacy outcome measures for this study are as follows:

- *Annualized rate of decline in 6-minute walk test (6MWT) distance over 52 weeks*
- *Time from randomization to first occurrence of a $\geq 10\%$ absolute decline in percentage of predicted FVC or death from any cause*
- *Annualized rate of decrease in percentage of predicted DL_{CO} over 52 weeks*
- *PFS, defined as the time from study treatment randomization to the first occurrence of any of the following disease progression or death events:*
 - Death from any cause
 - All cause hospitalization
 - A decrease from baseline (*relative change*) of $\geq 10\%$ in FVC (*mL/year*)
- *Annualized rate of decrease in FVC over a 52-week period (mL/year)*
- *Annualized rate of decrease in ATAQ-IPF total score over a 52-week period*
- *Time from randomization to first occurrence of the SGRQ worsening (total score) as defined by reaching MID: Total Score = 7 or death from any cause*
- *Time from randomization to non-elective hospitalization or death from any cause*
- *Time from randomization to first event of acute IPF exacerbation as defined below*
IPF exacerbation is defined as an event that meets all of the following criteria as determined by the investigator:
 - Unexplained worsening or development of dyspnea within the previous 30 days*

Appendix 1 Protocol Synopsis (cont.)

***And** radiologic evidence of new bilateral ground-glass abnormality or consolidation superimposed on a reticular or honeycomb background pattern that is consistent with UIP*

***And** absence of alternative causes, such as left heart failure, pulmonary embolism, pulmonary infection (on the basis of endotracheal aspirate or bronchoalveolar lavage, if available, or investigator judgment), or other events leading to acute lung injury (e.g., sepsis, aspiration, trauma, reperfusion pulmonary edema)*

Safety Outcome Measures

All safety outcome measures will be assessed by comparing results from the lebrikizumab treatment group with the placebo group. The safety outcome measures for this study are as follows:

- Frequency of adverse events during the study
- Severity of adverse events during the study
- Incidence of anti-therapeutic antibodies (ATAs) against lebrikizumab throughout the study

Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Serum lebrikizumab concentration at Week 52 (C_{Wk52})
- Predose serum lebrikizumab concentrations (C_{min}) at Weeks 4, 12, 24, and 36 ($C_{min,Wk4}$, $C_{min,Wk12}$, $C_{min,Wk24}$, and $C_{min,Wk36}$)
- Elimination half-life of lebrikizumab

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Change from baseline to Week 52 in radiographic findings on pulmonary HRCT, including QLF score
- *Change from screening (corresponding to timing for randomization strata) in serum and plasma biomarkers (e.g., periostin and CCL18) and change from baseline in serum and plasma biomarkers (e.g., periostin, chemokine (C-C motif) ligand 18 [CCL18], YKL40, COMP, OPN, CCL13)*
- Serum lebrikizumab concentrations during the extended treatment and the 14-week safety follow-up period
- Exposure-response relationships (to be evaluated as warranted)
- Change from baseline to Week 52 in the Borg CR10 Scale
- *Change from baseline to Week 52 in the ATAQ-IPF*
- *Time from randomization to first occurrence of SGRQ individual domain worsening as defined by reaching MID: Symptom = 8, Activity = 5, Impact = 7, or death from any cause*
- *Change from baseline to Week 52 in the SGRQ*

The analysis plan for the exploratory HRCT and biomarkers will be specified in a separate document.

Appendix 1

Protocol Synopsis (cont.)

Investigational Medicinal Products

Test Product

Lebrikizumab will be administered by subcutaneous injection of 250 mg every 4 weeks, with the first injection occurring at the randomization visit (Day 1, Visit 2). Patients will continue to receive blinded study treatment every 4 weeks during the placebo-controlled treatment period for a total of 13 doses/26 injections of blinded treatment.

Comparator

For patients in Cohort A, placebo will be administered. For patients in Cohort B, placebo plus a pirfenidone background dose of ≤ 2403 mg/d will be administered in divided doses three times per day with food.

Statistical Methods

Primary Analysis

The analysis of data from the placebo-controlled period *for each cohort* will be performed when all patients have either completed the *end of the placebo-controlled treatment (Week 52/EOT)* visit or discontinued early from the study. Treatment assignment will be unblinded to the personnel performing the analysis when all data through the EOT visit are in the database and the data have been cleaned and verified *for each cohort*.

The analysis of complete data for the study, including data from the placebo-controlled period, open-label extension period for Cohort A, and the 14-week safety follow-up period, will be performed when all patients have either completed the placebo-controlled period, open-label extension period for Cohort A, and 14-week safety follow-up period or discontinued early from the study, all data from the study are in the database, and the database is locked. *An interim futility analysis of Cohort B was conducted.*

Efficacy Analyses

The analysis of data from the treatment period in Cohort A will be performed when all patients enrolled in Cohort A have either completed the end of placebo controlled treatment visit (Week 52), or discontinued early from the study. Treatment assignment will be unblinded to the personnel performing the analysis when all data through the Week 52 visit are in the database and the data have been cleaned and verified.

The analysis of data from the treatment period in Cohort B will be performed when all patients enrolled in Cohort B have either completed the end of treatment visit (Week 52) or discontinued early from the study. Treatment assignment will be unblinded to the personnel performing the analysis when all data through the Week 52 visit are in the database and the data have been cleaned and verified.

However, the Sponsor study team directly involved in the study conduct (medical monitoring, clinical operations, drug safety, etc.) will not have access to individual treatment assignments until study completion, when all patients have completed the safety follow-up or discontinued the study. All non-Sponsor personnel who are involved in the conduct of the study (e.g., patients, site monitors, and investigators) will remain blinded to patient-specific treatment assignments until all patients complete the safety follow-up period or discontinue from the study. Complete details of the analysis will be provided in the SAP, which will be finalized prior to unblinding the data.

Safety Analyses

Safety analyses will be based on all patients who received at least one dose of *randomized* study drug, with patients grouped according to the actual treatment received. Safety summaries will be presented by treatment arm for all treated patients. *In addition, safety listings will be provided for any events reported during pirfenidone exposure prior to randomization.*

Appendix 1 Protocol Synopsis (cont.)

Safety will be assessed through the summary of adverse events, laboratory test results, (including antibodies to lebrikizumab), ECG, and vital signs. These summaries will be produced separately for *each cohort* for the treatment period (placebo-controlled study treatment period, the *Cohort A* open-label lebrikizumab period).

Pharmacokinetic Analyses

Individual and mean serum lebrikizumab concentration-versus-time data will be reported. *During the treatment period*, mean concentrations will be reported at Weeks 4, 12, 24, 36, and 52 ($C_{\min, \text{Wk}4}$, $C_{\min, \text{Wk}12}$, $C_{\min, \text{Wk}24}$, $C_{\min, \text{Wk}36}$, $C_{\text{Wk}52}$, respectively). Estimates for these parameters will be tabulated and summarized (mean, SD, coefficient of variation, median, minimum, and maximum). Additional PK analyses during the treatment period or the safety follow-up period may be conducted as appropriate. Population PK modeling may be performed to characterize inter-individual variability, which may be reported separately from the clinical study report.

Exploratory Analyses

Analysis of exploratory efficacy endpoints will be described in the Statistical Analysis Plan. Several pharmacodynamic biomarkers have been identified (e.g., periostin, CCL18, YKL40, COMP, OPN, CCL13) and will be measured in serum or plasma samples to assess the effect of lebrikizumab on these biomarkers. Exploratory exposure-response analysis will be performed as appropriate.

Determination of Sample Size

In Cohort A, a sample size of 75 patients in each treatment group will provide *approximately 80%* power to detect a *change in the annualized rate of decline in percentage of predicted FVC over 52 weeks of a 3.7%* difference in the means of the absolute change from baseline in percentage of predicted FVC at 52 weeks, assuming that the common standard deviation is 8% (as reported in the placebo group in the ASCEND trial of pirfenidone) using a two group t-test with a 0.05 two-sided significance level.

In Cohort B, a sample size of 165 patients in each treatment group will provide *approximately 80%* power to detect a 2.5% difference in the *annualized rate of decline* in percentage of predicted FVC *over 52 weeks*, assuming that the common standard deviation is 8% (as reported in the ASCEND trial of pirfenidone) using a two group t-test with a 0.05 two-sided significance level.

Optional Interim Analyses

The Sponsor may choose to conduct up to two interim efficacy analyses. Interim analyses will involve unblinding of treatment assignments to the Sponsor for purposes of data analysis and interpretation. Patients and all study site personnel will remain blinded to individual patient-level treatment assignments until completion of the trials. The decision to conduct optional interim analyses and the timing of the analyses will be documented in the Sponsor's trial master file prior to the conduct of the interim analyses. The interim analyses 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.

After the analysis of Cohort A, the Sponsor formed an IMC to perform an unplanned interim futility analysis of Cohort B to determine if it should be terminated for lack of sufficient efficacy. Following this analysis, the decision was made to continue the study and not perform additional efficacy and/or futility interim analyses.

Appendix 2

Schedule of Assessments: Screening and Placebo Controlled Treatment Period - Cohort A

	Screening	Rand.	Placebo Controlled Study Treatment Period ^a														EOT ^{a, b}	ET ^a	UV
Week	—	0	1	4	8	12	16	20	24	28	32	36	40	44	48	52	—	—	
Day (Window)	-28	1	8 (±2)	29 (±3)	57 (±3)	85 (±3)	113 (±3)	141 (±3)	169 (±3)	197 (±3)	225 (±3)	253 (±3)	281 (±3)	309 (±3)	337 (±3)	365 (±3)	—	—	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	—	—	
Informed consent ^c	x																		
Demographic data	x																		
Medical history	x																		
Physical exam ^d	x																		
Limited physical examination ^d		x														x	x	x	
Weight	x					x			x			x			x	x	x		
Height	x																		
Vital signs ^e	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Resting pulse oximetry	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Single ECG ^f	x								x							x	x		
Spirometry	x ^g	x	x	x		x			x			x		x		x	x	x	
DL _{CO} (mL CO/min-1/mmHg-1)	x	x	x	x		x			x			x		x		x	x	x	
HRCT ± SLB central review for eligibility ^h	x																		
Quantitative HRCT ⁱ	x															x	x		

Appendix 2
Schedule of Assessments: Screening and Placebo Controlled Treatment Period - Cohort A (cont.)

	Screening	Rand.	Placebo Controlled Study Treatment Period ^a													EOT ^{a, b}	ET ^a	UV
Week	—	0	1	4	8	12	16	20	24	28	32	36	40	44	48	52	—	—
Day (Window)	-28	1	8 (±2)	29 (±3)	57 (±3)	85 (±3)	113 (±3)	141 (±3)	169 (±3)	197 (±3)	225 (±3)	253 (±3)	281 (±3)	309 (±3)	337 (±3)	365 (±3)	—	—
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	—	—
6MWT/Borg CR10 Scale ^j	x	x							x							x	x	
ATAQ-IPF ^k		x		x		x			x			x				x	x	
SGRQ ^k		x		x		x			x			x				x	x	
EQ-5D ^k		x		x		x			x			x				x	x	x
Hematology ^l	x	x		x	x	x			x			x			x	x	x	x
Chemistry ^m	x	x		x	x	x			x			x			x	x	x	x
B-type natriuretic peptide	x																	
Urinalysis ⁿ	x	x				x			x			x				x	x	
Serum pregnancy test ^o	x																	
Urine pregnancy test ^o		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Serum PK sample ^p		x	x	x		x			x			x				x	x	

Appendix 2

Schedule of Assessments: Screening and Placebo Controlled Treatment Period - Cohort A (cont.)

	Screening	Rand.	Placebo Controlled Study Treatment Period ^a													EOT ^{a, b}	ET ^a	UV
Week	—	0	1	4	8	12	16	20	24	28	32	36	40	44	48	52	—	—
Day (Window)	-28	1	8 (±2)	29 (±3)	57 (±3)	85 (±3)	113 (±3)	141 (±3)	169 (±3)	197 (±3)	225 (±3)	253 (±3)	281 (±3)	309 (±3)	337 (±3)	365 (±3)	—	—
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	—	—
Plasma PD sample ^{p, q}		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum PD sample ^{p, q}	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum antibodies ^p		x		x		x			x			x				x	x	
Serum tryptase ^r																		
Optional DNA sample ^s		x																
Optional RNA sample ^s		x	x						x							x		
Study drug administration ^t		x ^r		x ^r	x ^r	x	x	x	x	x	x	x	x	x	x			
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events ^{d, u}	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Notes: On treatment days, all assessments should be performed prior to dosing unless otherwise specified.

6MWT=6-minute walk test; ATAQ-IPF=A Tool to Assess Quality of Life in IPF; Borg CR10=Borg Category Ratio 10 Scale[®]; DL_{CO}=diffusion capacity of the lung for carbon monoxide; ECG=electrocardiogram; EOT=end of treatment; EQ-5D=EuroQol 5-Dimension Questionnaire;

Appendix 2

Schedule of Assessments: Screening and Placebo Controlled Treatment Period - Cohort A (cont.)

ET=early termination; HRCT=high-resolution computed tomography; IPF=idiopathic pulmonary fibrosis; Rand. = randomization; SGRQ= St George's Respiratory Questionnaire; UV=unscheduled visit.

- ^a Patients who discontinue study drug are encouraged to remain in the study and complete all scheduled assessments. If this is not feasible, the patient should enter and complete the safety follow-up period or the early termination assessments, unless consent has been withdrawn. If a patient is unable or unwilling to complete the assessment for 6MWT and/or the qtHRCT substudy assessment this will not be considered a protocol deviation.
- ^b Patients who enter the open label lebrikizumab treatment period should complete Day1 OL visit 35 on the same day.
- ^c Informed consent may be obtained on the day of Visit 1 or prior to visit 1 at the discretion of the investigator. The informed consent process must be completed before initiating any Visit 1 assessments.
- ^d Record abnormalities observed at baseline on the Medical History and Baseline Conditions eCRF. New or worsening abnormalities should be recorded on the Adverse Event eCRF.
- ^e Respiratory rate, pulse rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature.
- ^f ECGs should be performed prior to any scheduled study procedures (e.g., vital sign measurements, blood draws, and study drug administration, if applicable).
- ^g Both pre- and post-bronchodilator testing are required at screening, but only pre-bronchodilator pulmonary function test is required throughout other study visits.
- ^h A Multidisciplinary Discussion of Diagnosis (MDD) based on 2011 ATS/ERS/JRS/ALAT guidelines will be utilized to finalize the diagnosis in the event the initial central review outcome results for HRCT and SLB are disparate (inconsistent with usual interstitial pneumonitis (UIP)/definite UIP).
- ⁱ Optional procedure for patients who have consented to participate in the HRCT substudy limited to the United States and selected countries. Baseline qtHRCT scan does not need to be repeated if one was performed as part of the eligibility assessment. All patients enrolled in the substudy will have an additional qtHRCT scan performed at the EoT Visit 16 at Week 52. Assessment at ET is requested but not considered a protocol deviation if the patient is unable or unwilling to perform.
- ^j The Borg CR10 Scale will be performed immediately before and after the 6MWT. Assessment of the 6MWT and Borg CR10 Scale at ET is requested but not considered a protocol deviation if the patient is unable or unwilling to perform.
- ^k Complete before all other non-PRO assessments and before the patient receives any disease-status information or study treatment during the study visit.
- ^l Includes RBC count, WBC count, hemoglobin, hematocrit, platelet count, and WBC differential count (neutrophils, bands, lymphocytes, eosinophils, basophils, monocytes, and other cells).

Appendix 2

Schedule of Assessments: Screening and Placebo Controlled Treatment Period - Cohort A (cont.)

- ^m Includes sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase, creatinine phosphokinase, and uric acid. **Any patient who starts rescue therapy (including but not limited to pirfenidone) will need monitoring per the prescribing information.** All safety laboratory assessments, including those required for the prescribed rescue medication, should be analyzed by the central laboratory utilized for the GB28547 clinical study.
- ⁿ Includes protein, blood, glucose, and microscopic examination (RBC, WBC, casts, and crystals).
- ^o Only for women of childbearing potential see Appendix 9.
- ^p On dosing days. Samples for serum PK, PD, antibody (including anti-therapeutic antibody), and optional PAXgene mRNA analysis will be taken prior to dosing. An additional sample for serum antibody and PK analysis must be taken in the event of an anaphylactic, anaphylactoid, or serious hypersensitivity reaction. PLB2 antibody testing may be performed as appropriate using serum samples collected at pre-specified timepoints.
- ^q Includes IL-13– or IPF-related biomarkers (e.g., periostin, CCL18, YKL40, COMP, OPN, CCL13). Screening serum periostin sample should be collected and shipped to the central laboratory within the first 2 weeks of screening.
- ^r Whenever possible, patients who experience an acute onset of symptoms of an anaphylactic, anaphylactoid, or serious hypersensitivity reaction should have a blood sample for total serum tryptase analysis collected 1–6 hours after the event. The tryptase sample will be collected and analyzed per the site's local laboratory practice.
- ^s The DNA sample and whole blood PAXgene mRNA samples are optional and should be obtained only from patients who sign the separate RCR Informed Consent Form.
- ^t Patients will remain in the clinic for 1 hour after dosing for the first three dosing visits and for 30 minutes after dosing on all other study drug administration days for routine safety monitoring.
- ^u All adverse events including serious adverse events and adverse events of special interest.

Appendix 3

Schedule of Assessments: Open-Label Lebrikizumab Treatment Period - Cohort A

Week	Wk 52 (Day1 OL)	Wk 56 (Wk4 OL)	Wk 60 (Wk8 OL)	Wk 64 (Wk12 OL)	Wk 68 (Wk16 OL)	Wk 72 (Wk20 OL)	Wk 76 (Wk24 OL)	Wk 80 (Wk28 OL)	Wk84 (Wk32 OL)	Wk 88 (Wk36 OL)	Wk92 (Wk40 OL)	Wk96 (Wk44 OL)	Wk100 (Wk48 OL)	Wk104 (Wk52 OL)		
Day (Assessment Window)	365 (1OL) (± 3)	393 (29OL) (± 3)	421 (57OL) (± 3)	449 (85OL) (± 3)	477 (13OL) (± 3)	505 (141 OL) (± 3)	533 (169 OL) (± 3)	561 (197 OL) (± 3)	589 (225 OL) (± 3)	617 (253 OL) (± 3)	645 (281 OL) (± 3)	673 (309 OL) (± 3)	701 (337 OL) (± 3)	729 (365 OL) (± 3)		
Visit	35	36	37	38	39	40	41	42	43	44	45	46	47	EoT ^b /SFU Wk4	ET ^q	UV
Limited physical exam ^a														x	x	x
Weight				x			x			x				x	x	
Vital signs ^c		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Resting Pulse Oximetry		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Single ECG ^d														x	x	
Spirometry		x	x	x			x			x			x	x	x	x
DLco		x	x	x			x			x			x	x	x	x
6MWT/BorgCR10 ^e							x							x	x	
ATAQ-PF ^f							x							x	x	
SGRQ ^f							x							x	x	
EQ-5D ^f							x							x	x	x

Appendix 3

Schedule of Assessments: Open-Label Lebrigizumab Treatment Period - Cohort A (cont.)

Week	Wk 52 (Day1 OL)	Wk 56 (Wk4 OL)	Wk 60 (Wk8 OL)	Wk 64 (Wk12 OL)	Wk 68 (Wk16 OL)	Wk 72 (Wk20 OL)	Wk 76 (Wk24 OL)	Wk 80 (Wk28 OL)	Wk84 (Wk32 OL)	Wk 88 (Wk36 OL)	Wk92 (Wk40 OL)	Wk96 (Wk44 OL)	Wk100 (Wk48 OL)	Wk104 (Wk52 OL)		
Day (Assessment Window)	365 (1OL) (± 3)	393 (29OL) (± 3)	421 (57OL) (± 3)	449 (85OL) (± 3)	477 (13OL) (± 3)	505 (141 OL) (± 3)	533 (169 OL) (± 3)	561 (197 OL) (± 3)	589 (225 OL) (± 3)	617 (253 OL) (± 3)	645 (281 OL) (± 3)	673 (309 OL) (± 3)	701 (337 OL) (± 3)	729 (365 OL) (± 3)		
Visit	35	36	37	38	39	40	41	42	43	44	45	46	47	EoT ^b /SFU Wk4	ET ^q	UV
Hematology ^g		x	x		x		x		x		x		x	x	x	x
Chemistry ^h		x	x		x		x		x		x		x	x	x	x
Urinalysis ⁱ		x	x		x		x		x		x		x	x	x	
Urine pregnancy ^j		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Serum PK ^k				x			x			x				x	x	
Plasma PD sample ^{k,l}		x	x	x			x			x			x	x	x	x
Serum PD ^{k,l}		x	x	x			x			x			x	x	x	x
Serum antibodies ^k		x		x			x							x	x	
Serum Tryptase ^m																
Optional RNA ⁿ				x			x							x		
Study drug administration ^{o,p}	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Concomitant medications ^q		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events ^{a,q}		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 3

Schedule of Assessments: Open-Label Lebrikizumab Treatment Period - Cohort A (cont.)

6MWT=six minute walk test; ATAQ-IPF= A Tool to Assess Quality of Life in IPF; Borg CR10 Scale = Borg Category Ratio 10 Scale[®]; CTD=connective-tissue disease; DL_{CO}=diffusion capacity of the lung for carbon monoxide; eCRF =electronic Case Report Form; EOMT =end of minimum treatment; EOT=end of treatment; EQ-5D =EuroQol 5-Dimension Questionnaire; ET=early termination; FEV₁=forced expiratory volume in 1 second; FVC=forced vital capacity; HRCT=high-resolution computed tomography; IL-13=interleukin 13; IPF=idiopathic pulmonary fibrosis; PD=pharmacodynamic; PK=pharmacokinetic; Rand.=Randomization; SGRQ=St. George's Respiratory Questionnaire; UV=unscheduled visit.

Notes: On treatment days, all assessments should be performed prior to dosing unless otherwise specified.

- ^a New or worsening abnormalities should be recorded on the Adverse Event eCRF.
- ^b This visit replaces Safety Follow-up Visit 1 on [Appendix 4](#). The next visit is Safety Follow-up Visit 2 at Week 12 (12 weeks after last dose of study drug).
- ^c Respiratory rate, pulse rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature.
- ^d ECGs should be performed prior to any scheduled study procedures (e.g., vital sign measurements, blood draws, and study drug administration, if applicable).
- ^e The Borg CR10 Scale will be performed immediately before and after the 6MWT.
- ^f Complete before all other non-PRO assessments and before the patient receives any disease-status information or study treatment during the study visit.
- ^g Includes RBC count, WBC count, hemoglobin, hematocrit, platelet count, and WBC differential count (neutrophils, bands, lymphocytes, eosinophils, basophils, monocytes, and other cells).
- ^h Includes sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase, creatinine phosphokinase, and uric acid. Any patient who starts rescue therapy (including but not limited to pirfenidone) will need monitoring per the prescribing information. All safety laboratory assessments, including those required for the prescribed rescue medication, should be analyzed by the central laboratory utilized for the GB28547 clinical study.
- ⁱ Includes protein, blood, glucose, and microscopic examination (RBC, WBC, casts, and crystals).
- ^j Only for women of childbearing potential see Appendix 9.
- ^k On dosing days. Samples for serum PK, PD, antibody (including anti-therapeutic antibody), and optional PAXgene mRNA analysis will be taken prior to dosing. An additional sample for serum antibody and PK analysis must be taken in the event of an anaphylactic, anaphylactoid, or serious hypersensitivity reaction. PLB2 antibody testing may be performed as appropriate using serum samples collected at pre-specified timepoints.
- ^l Includes IL-13 or IPF-related biomarkers (e.g., periostin, CCL18, YKL40, COMP, OPN, CCL13).
- ^m Whenever possible, patients who experience an acute onset of symptoms of an anaphylactic, anaphylactoid, or serious hypersensitivity reaction should have a blood sample for total serum tryptase analysis collected 1–6 hours after the event. The tryptase sample will be collected and analyzed per the site's local laboratory practice.

Appendix 3

Schedule of Assessments: Open-Label Lebrikizumab Treatment Period - Cohort A (cont.)

- ⁿ The whole blood PAXgene mRNA samples are optional and should be obtained only from patients who sign the separate RCR Informed Consent Form.
- ^o Patients will remain in the clinic for 1 hour after dosing for the first three dosing visits and for 30 minutes after dosing on all other study drug administration days for routine safety monitoring.
- ^p Patients who discontinue study drug are encouraged to remain in the study and complete all scheduled assessments. If this is not feasible, the patient should enter and complete the safety follow-up period or the early termination assessments, unless consent has been withdrawn.
- ^q All adverse events including serious adverse events and adverse events of special interest.

Appendix 4
Schedule of Assessments: Screening, Pirfenidone Titration Run-In, and Placebo-Controlled Treatment Period - Cohort B

	Screening	PFD titration -run-in	Rand.	Placebo controlled Study Treatment Period ^a													EOT ^{a, b}	ET ^a	UV
				1	4	8	12	16	20	24	28	32	36	40	44	48			
Week	—		0	1	4	8	12	16	20	24	28	32	36	40	44	48	52	—	—
Day (Window)	-28 (± 14)	4-6 wks (28-42 days)	1	8 (± 2)	29 (± 3)	57 (± 3)	85 (± 3)	113 (± 3)	141 (± 3)	169 (± 3)	197 (± 3)	225 (± 3)	253 (± 3)	281 (± 3)	309 (± 3)	337 (± 3)	365 (± 3)	—	—
Visit	1	1.5	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	—	—
Informed consent ^c	x																		
Demographic data	x																		
Medical history	x																		
Physical exam ^d	x																		
Limited physical examination ^d			x														x	x	x
Weight	x	x	x		x	x	x			x			x			x	x	x	
Height	x																		
Vital signs ^e	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Resting pulse oximetry	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Single ECG ^f	x									x							x	x	
Spirometry	x ^g		x	x	x		x			x			x		x		x	x	x

Appendix 4
Schedule of Assessments: Screening, Pirfenidone Titration Run-In, and Placebo-Controlled Treatment Period - Cohort B (cont.)

Week	Screening	PFD titration -run-in	Rand.	Placebo controlled Study Treatment Period ^a													EOT ^{a, b}	ET ^a	UV
				1	4	8	12	16	20	24	28	32	36	40	44	48			
Day (Window)	-28 (± 14)	4-6 wks (28-42 days)	1	8 (± 2)	29 (± 3)	57 (± 3)	85 (± 3)	113 (± 3)	141 (± 3)	169 (± 3)	197 (± 3)	225 (± 3)	253 (± 3)	281 (± 3)	309 (± 3)	337 (± 3)	365 (± 3)	—	—
Visit	1	1.5	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	—	—
DL _{co} (mL CO/min-1/m mHg-1)	x		x	x	x		x			x			x		x		x	x	x
HRCT ± SLB central review for eligibility ^h	x																		
Quantitative HRCT ⁱ	x																x	x	
6MWT/Borg CR10 Scale ^j	x		x							x							x	x	
ATAQ-IPF ^k	x	x	x		x		x			x			x				x	x	
SGRQ ^k	x	x	x		x		x			x			x				x	x	
EQ-5D ^k			x		x		x			x			x				x	x	x
Hematology ^l	x		x		x	x	x			x			x			x	x	x	x
Chemistry ^m	x	x ⁿ	x	x	x	x	x	x	x	x			x			x	x	x	x
B-type natriuretic peptide	x																		
Urinalysis ^o	x		x				x			x			x				x	x	

Appendix 4
Schedule of Assessments: Screening, Pirfenidone Titration Run-In, and Placebo-Controlled Treatment Period - Cohort B (cont.)

Week	Screening	PFD titration -run-in	Rand.	Placebo controlled Study Treatment Period ^a													EOT ^{a, b}	ET ^a	UV
				0	1	4	8	12	16	20	24	28	32	36	40	44			
Day (Window)	-28 (± 14)	4-6 wks (28-42 days)	1	8 (± 2)	29 (± 3)	57 (± 3)	85 (± 3)	113 (± 3)	141 (± 3)	169 (± 3)	197 (± 3)	225 (± 3)	253 (± 3)	281 (± 3)	309 (± 3)	337 (± 3)	365 (± 3)	—	—
Visit	1	1.5	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	—	—
Serum pregnancy test ^p	x																		
Urine pregnancy test ^p			x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum PK sample ^q			x	x	x		x			x			x				x	x	
Plasma PD sample ^{q, r}			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum PD sample ^{q, r}	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum antibodies ^q			x		x		x			x			x				x	x	
Serum tryptase ^s																			
Optional DNA sample ^t			x																
Optional RNA sample ^t			x	x						x							x		
Study drug administration ^u			x ^s		x ^s	x ^s	x	x	x	x	x	x	x	x	x	x			

Appendix 4

Schedule of Assessments: Screening, Pirfenidone Titration Run-In, and Placebo-Controlled Treatment Period - Cohort B (cont.)

	Screening	PFD titration -run-in	Rand.	Placebo controlled Study Treatment Period ^a														EOT ^{a, b}	ET ^a	UV
Week	—		0	1	4	8	12	16	20	24	28	32	36	40	44	48	52	—	—	
Day (Window)	-28 (± 14)	4-6 wks (28-42 days)	1	8 (± 2)	29 (± 3)	57 (± 3)	85 (± 3)	113 (± 3)	141 (± 3)	169 (± 3)	197 (± 3)	225 (± 3)	253 (± 3)	281 (± 3)	309 (± 3)	337 (± 3)	365 (± 3)	—	—	
Visit	1	1.5	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	—	—	
PFD dispensing		x	x		x	x	x	x	x	x	x	x	x	x	x	x	x			
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse events ^v	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	

6MWT=6-minute walk test; ATAQ-IPF=A Tool to Assess Quality of Life in IPF; Borg CR10=Borg Category Ratio 10 Scale®; DL_{CO}=diffusion capacity of the lung for carbon monoxide; ECG=electrocardiogram; EOT=end of treatment; EQ-5D=EuroQol 5-Dimension Questionnaire; ET=early termination; HRCT=high-resolution computed tomography; IPF=idiopathic pulmonary fibrosis; PFD=pirfenidone, Rand.=randomization; SGRQ=St. George's Respiratory Questionnaire; UV=unscheduled visit.

Notes: On treatment days, all assessments should be performed prior to dosing unless otherwise specified.

Appendix 4

Schedule of Assessments: Screening, Pirfenidone Titration Run-In, and Placebo-Controlled Treatment Period - Cohort B (cont.)

- ^a Patients who discontinue study drug are encouraged to remain in the study and complete all scheduled assessments. If a patient is unable or unwilling to complete the assessment for 6MWT and/or the qtHRCT substudy assessment this will not be considered a protocol deviation. If this is not feasible, the patient should enter and complete the safety follow-up period or the early termination assessments, unless consent has been withdrawn.
- ^b This visit replaces Safety Follow-up Visit 1 on [Appendix 4](#). The next visit is Safety Follow-up Visit 2 at Week 12.
- ^c Informed consent may be obtained on the day of Visit 1 or prior to visit 1 at the discretion of the investigator. The informed consent process must be completed before initiating any Visit 1 assessments.
- ^d Record abnormalities observed at baseline on the Medical History and Baseline Conditions eCRF. New or worsening abnormalities should be recorded on the Adverse Event eCRF.
- ^e Respiratory rate, pulse rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature.
- ^f ECGs should be performed prior to any scheduled study procedures (e.g., vital sign measurements, blood draws, and study drug administration, if applicable).
- ^g Both pre- and post-bronchodilator testing are required at screening, but only pre-bronchodilator pulmonary function test is required throughout other study visits.
- ^h A Multidisciplinary Discussion of Diagnosis (MDD) based on 2011 ATS/ERS/JRS/ALAT guidelines will be utilized to finalize the diagnosis in the event the initial central review outcome results for HRCT and SLB are disparate (inconsistent with usual interstitial pneumonitis (UIP)/definite UIP).
- ⁱ Optional procedure for patients who have consented to participate in the HRCT substudy limited to the United States. Baseline qtHRCT scan does not need to be repeated if one was performed as part of the eligibility assessment. All patients enrolled in the substudy will have an additional qtHRCT scan performed at the EOT Visit16 at Week 52. Assessment at ET visit is requested but not considered a protocol deviation if patient is unable or unwilling to perform.
- ^j The Borg CR10 Scale will be performed immediately before and after the 6MWT. Assessment of the 6MWT and Borg CR10 Scale at ET visit is requested but not considered a protocol deviation if patient is unable or unwilling to perform.
- ^k Complete before all other non-PRO assessments and before the patient receives any disease-status information or study treatment during the study visit.
- ^l Includes RBC count, WBC count, hemoglobin, hematocrit, platelet count, and WBC differential count (neutrophils, bands, lymphocytes, eosinophils, basophils, monocytes, and other cells).
- ^m Includes sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase, creatinine phosphokinase, and uric acid. **Any patient who starts rescue therapy (including but not limited to pirfenidone) will need monitoring per the prescribing information. All safety laboratory assessments, including those required for the prescribed rescue medication, should be analyzed by the central laboratory utilized for the GB28547 clinical study.**
- ⁿ If run-in period exceeds 4 weeks, follow pirfenidone guidance provided in the ESBRIET/PIRESPA package insert for liver function test.

Appendix 4

Schedule of Assessments: Screening, Pirfenidone Titration Run-In, and Placebo-Controlled Treatment Period - Cohort B (cont.)

- ° Includes protein, blood, glucose, and microscopic examination (RBC, WBC, casts, and crystals).
- ° Only for women of childbearing potential see Appendix 9.
- ° On lebrikizumab dosing days. Samples for serum PK, PD, antibody (including anti-therapeutic antibody), and optional PAXgene mRNA analysis will be taken prior to lebrikizumab dosing. An additional sample for serum antibody and PK analysis must be taken in the event of an anaphylactic, anaphylactoid, or serious hypersensitivity reaction. *Anti-PLB2* antibody testing may be performed as appropriate using serum samples collected at pre-specified timepoints.
- ° Includes IL-13- or IPF-related biomarkers (e.g., periostin, CCL18, YKL40, COMP, OPN, CCL13). Screening serum periostin sample should be collected and shipped to the central laboratory within the first 2 weeks of screening.
- ° Whenever possible, patients who experience an acute onset of symptoms of an anaphylactic, anaphylactoid, or serious hypersensitivity reaction should have a blood sample for total serum tryptase analysis collected 1–6 hours after the event. The tryptase sample will be collected and analyzed per the site's local laboratory practice.
- ° The DNA sample and whole blood PAXgene mRNA samples are optional and should be obtained only from patients who sign the separate RCR Informed Consent Form.
- ° Patients will remain in the clinic for 1 hour after dosing for the first three dosing visits and for 30 minutes after dosing on all other study drug administration days for routine safety monitoring.
- ° All adverse events including serious adverse events and adverse events of special interest.

Appendix 5 Schedule of Assessments: Safety Follow-Up Period

WEEK post last dose	4 ^a	12	18 (final visit)
Day post last dose (assessment window)	28 (± 3)	84 (± 3)	126 (± 3)
Visit	SFU1	SFU2	SFU3
Limited physical exam ^b	x		x
Weight	x		x
Vital signs ^c	x	x	x
Resting pulse oximetry	x	x	x
Single ECG (all patients) ^d	x		x
Spirometry ⁱ	x	x	x
DLco	x	x	x
6MWT/BorgCR10 ^e	x		
ATAQ-IPF ^f	x		x
SGRQ ^f	x		x
EQ-5D ^f	x		x
Hematology ^g	x	x	x
Chemistry ^h	x	x	x
Urinalysis ⁱ	x		
Urine pregnancy test ^j	x		
Serum PK sample ^k	x	x	x
Plasma PD sample ^{k,l}	x	x	x
Serum PD sample ^{k,l}	x	x	x
Serum antibodies ^k	x		x

Appendix 5 Schedule of Assessments: Safety Follow-Up Period (cont.)

WEEK post last dose	4 ^a	12	18 (final visit)
Day post last dose (assessment window)	28 (± 3)	84 (± 3)	126 (± 3)
Visit	SFU1	SFU2	SFU3
Optional RNA sample ^m	x		
Concomitant medications	x	x	x
Adverse events ^{a,n}	x	x	x
PFD dispensing (Cohort B only)	x	x	

6MWT = 6-minute walk test; ATAQ-IPF = A Tool to Assess Quality of Life in IPF; Borg CR10 = Borg Category Ratio 10 Scale®; DL_{CO} = diffusion capacity of the lung for carbon monoxide; ECG = electrocardiogram; EOT = end of treatment; EQ-5D = EuroQol 5-Dimension Questionnaire; ET = early termination; HRCT = high-resolution computed tomography; IPF = idiopathic pulmonary fibrosis; SGRQ = St. George's Respiratory Questionnaire; UV = unscheduled visit.

- ^a For patients in Cohort A who only complete the placebo controlled study period at Week 52 and choose to discontinue, the Week 52 visit will count as this visit. For patients in Cohort A who complete the open-label lebrikizumab study period at week 52OL, the Week 52OL will count as this visit. For patients in Cohort B who complete the placebo controlled study period at Week 52, the Week 52 visit will count as this visit.
- ^b New or worsening abnormalities should be recorded on the Adverse Event eCRF.
- ^c Respiratory rate, pulse rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature.
- ^d ECGs should be performed prior to any scheduled study procedures (e.g., vital sign measurements, blood draws, and study drug administration, if applicable).
- ^e The Borg CR10 Scale will be performed immediately before and after the 6MWT.
- ^f Complete before all other non-PRO assessments and before the patient receives any disease-status information or study treatment during the study visit.
- ^g Includes RBC count, WBC count, hemoglobin, hematocrit, platelet count, and WBC differential count (neutrophils, bands, lymphocytes, eosinophils, basophils, monocytes, and other cells).

Appendix 5 Schedule of Assessments: Safety Follow-Up Period (cont.)

- ^h Includes sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase, creatinine phosphokinase, and uric acid. **Any patient who starts rescue therapy (including but not limited to pirfenidone) will need monitoring per the prescribing information.** All safety laboratory assessments, including those required for the prescribed rescue medication, should be analyzed by the central laboratory utilized for the GB28547 clinical study.
- ⁱ Includes protein, blood, glucose, and microscopic examination (RBC, WBC, casts, and crystals).
- ^j Only for women of childbearing potential see Appendix 9.
- ^k On lebrikizumab dosing days. Samples for serum PK, PD, antibody (including anti-therapeutic antibody), and optional PAXgene mRNA analysis will be taken prior to lebrikizumab dosing. An additional sample for serum antibody and PK analysis must be taken in the event of an anaphylactic, anaphylactoid, or serious hypersensitivity reaction. *Anti*-PLB2 antibody testing may be performed as appropriate using serum samples collected at pre-specified timepoints.
- ^l Includes IL-13- or IPF-related biomarkers (e.g., periostin, CCL18, YKL40, COMP, OPN, CCL13).
- ^m The whole blood PAXgene mRNA samples are optional and should be obtained only from patients who sign the separate RCR Informed Consent Form.
- ⁿ All adverse events including serious adverse events and adverse events of special interest.

Appendix 6 GAP Index and Staging System for IPF

The GAP index is an IPF disease staging system consisting of points ranging from 0 to 8 that correspond to increasing disease severity as outlined below.

	Predictor	Points
G	Gender	
	Female	0
	Male	1
A	Age (years)	
	≤60	0
	61–65	1
	>65	2
P	Physiology	
	FVC, % predicted	
	>75	0
	50–75	1
	≤49	2
	DLco, % predicted	
	>55	0
	36–55	1
	≤35	2
Cannot perform	3	
Total possible points		8

Stage	I	II	III
Points	0–3	4–5	6–8
Mortality			
1-year	5.6	16.2	39.2
2-year	10.9	29.9	62.1
3-year	16.3	42.1	76.8

Notes: GAP=gender, age, and two lung physiology variables (FVC and DLco). Patients should be scored in the “Cannot perform” category for DLco if their symptoms or lung function prohibited performance of the DLco maneuver. If DLco is unavailable because it was not ordered or not completed because of nonrespiratory limitations, then the model cannot be applied.

Source: Ley B, Ryerson CJ, Vittinghoff E, et al. A multidimensional index and staging system for idiopathic pulmonary fibrosis. *Annals of Internal Medicine* 2012; 156: 684–691.

Appendix 7

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 is 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), defined in adults as systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that person's baseline.