STATISTICAL ANALYSIS PLAN (SAP)

Study treatments: GB0139 3mg, GB0139 10mg, Placebo

Study Phase: Phase 2b

Study Title: GALACTIC-1 - A randomized, double-blind, multicentre, parallel, placebo-controlled Phase 2b study in subjects with idiopathic pulmonary fibrosis (IPF) investigating the efficacy and safety of GB0139, an inhaled galectin-3 inhibitor administered via a dry powder inhaler over 52 weeks

SAP Version Number: Version 1
Date: 07 July 2023
Author: [redacted]
Principal Statistician, Statistics
[redacted]

APPROVAL SIGNATURES FOR SAP

Study Title: GALACTIC-1 - A randomized, double-blind, multicentre, parallel, placebo-controlled Phase 2b study in subjects with idiopathic pulmonary fibrosis (IPF) investigating the efficacy and safety of GB0139, an inhaled galectin-3 inhibitor administered via a dry powder inhaler over 52 weeks

Protocol Number:	GALACTIC-1
EudraCT Number/IND Number:	2018-002664-73 / 124075
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This Statistical Analysis Plan was subject to critical review and complies with the statistical principles set out in ICH guidelines E3, E6 and E9 and Plus-Project Standard Operating Procedure (SOP)-BIO-002 Development of Statistical Analysis Plans.

Prepared by:

[redacted] 07 Jul 2023
Date (DDMONYYYY)

Reviewed by:

[redacted]
Date (DDMONYYYY)

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Prepared by:

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07 JUL 2023

Date (DDMONYYYY)

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LIST OF ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemistry
BID	Twice-daily
BDRM	Blinded Data Review Meeting
BMI	Body Mass Index
BUN	Blood urea nitrogen
CI	Confidence interval
CRF	Case report form (electronic/paper)
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DBL	Database Lock
DMP	Data Management Plan
DSMB	Data Safety Monitoring Board
EoS	End of Study
EoT	End of Treatment
FV	Final Visit
Hb	Hemoglobin
HCT	Hematocrit
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IPF	Idiopathic Pulmonary Fibrosis
ITT	Intention-to-treat
LLOD	Lower Limit of Detection
LLOQ	Lower Limit of Quantification
MACE	Major Adverse Cardiovascular Event
MedDRA	Medical dictionary for regulatory activities
mITT	Modified intention-to-treat
PPS	Per protocol set
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SoC	Standard of Care
SOC	System Organ Class
SOP	Standard Operating Procedure
SS	Safety Set
TEAE	Treatment emergent adverse event
TFL	Tables, Figures and Listings
ULN	Upper Limit of Normal
ULOD	Upper Limit of Detection
ULOQ	Upper Limit of Quantification
WHO-DD	World Health Organisation Drug Dictionary

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under protocol GALACTIC-1 (EudraCT Number 2018-002664-73 / IND 124075).

This SAP should be read in conjunction with the Clinical Study Protocol (CSP). This version of the plan has been developed using CSP version 7.0 dated 28 January 2022 [1] and Case Report Form (CRF) version 156 dated Nov 2021 [2]. Any further changes to these documents may necessitate updates to the SAP.

1.1 Trial design

A randomized, double-blind, multicentre, parallel, placebo-controlled phase 2b study in subjects with idiopathic pulmonary fibrosis (IPF). All subjects enrolled into the study should have a diagnosis of IPF established within the previous five years, and a diagnostic HRCT scan assessed by central independent radiologists according the ATS/ERS/Fleischner criteria available within the previous 12 months prior to screening.

The original design consisted of 3 treatment groups, placebo, GB0139 3mg and GB0139 10mg, with patients randomized in a 1:1:1 ratio. Stratification in the original version of the study was according to the patient's standard of care treatment at enrollment;

- SoC1 being patients currently treated with either pirfenidone or nintedanib,
- SoC2 being patients not currently treated with pirfenidone or nintedanib.

A subject's SoC must have been deemed as stable by the Principal Investigator or treating physician before their enrollment in the study.

It was initially planned to randomize approximately 450 patients to this design across approximately 70 sites from the European Union and 30 sites from the United States. This design was intended to evaluate the efficacy and safety of GB0139 over 52 weeks of dosing in addition to the subject's current standard of care (SoC) (including treatment with either pirfenidone or nintedanib). It was planned to continue blinded treatment beyond week 52 and up to week 104 to provide further safety follow-up information.

Following a review of unblinded efficacy and safety data by the study's DSMB in February 2021, the study design has been modified based on the DSMB's recommendation. Participants randomized to the 10mg GB0139 group, and all those taking nintedanib or pirfenidone, have been discontinued from the study. In addition, subjects who had already

completed 52 weeks of treatment were discontinued. In total, about 320 subjects had been randomized under the original design, and approximately 200 were discontinued.

In the revised version of the study, post the changes following the DSMB recommendations, participants who are not taking nintedanib or pirfenidone at screening and during the study continue in the study. New patients are recruited and randomized to receive either 3mg GB0139 or placebo in a 2:1 ratio, to ensure the same proportion of patients on active drug as in the original design. Approximately 141 patients are expected to be enrolled into the modified design. Both nintedanib and pirfenidone are prohibited in the revised version of the study.

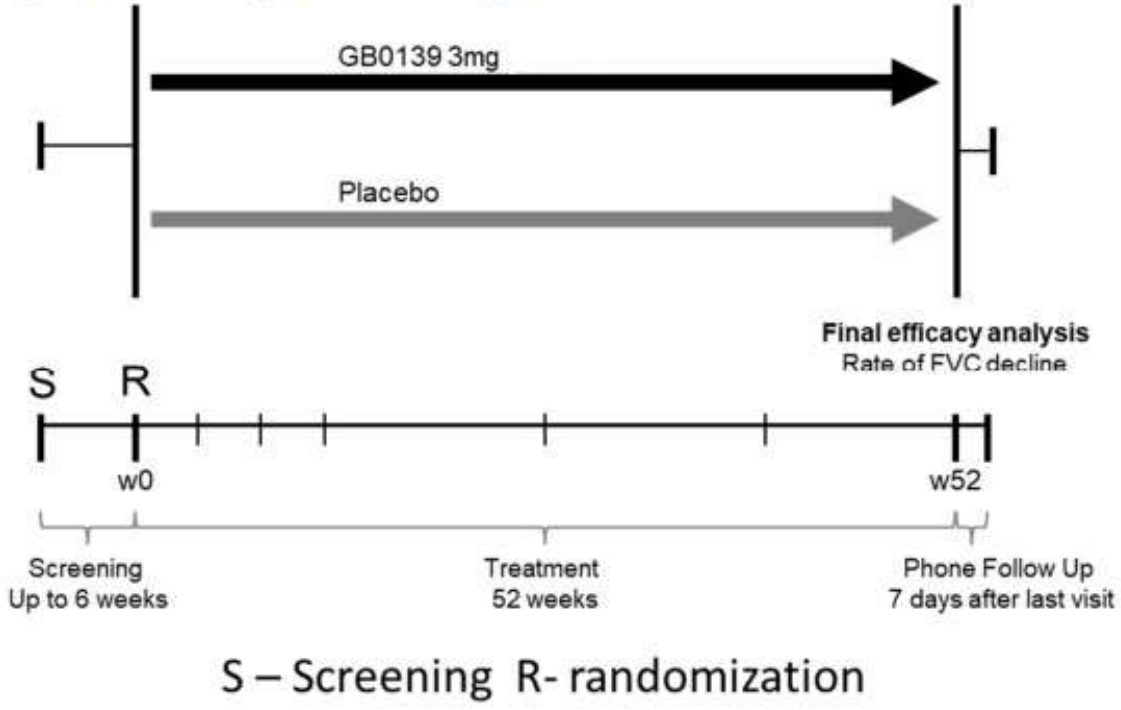
The revised study design consists of a screening period up to 6 weeks, a 52-week double-blind treatment period and a safety follow-up call 7 days post last visit. The duration of the entire trial for each subject will be approximately 59 weeks from first screening to the final safety follow up.

After giving Informed Consent, the subject may be selected for the study at Visit 1. Subjects who fail screening may be permitted to undergo re-screening one additional time. If they are successfully re-screened then they will be allocated a new unique subject ID number. If all exclusion and inclusion criteria are fulfilled then randomization occurs at Visit 2 (Week 0). Further visits are scheduled at Week 4 (V3), Week 8 (V4), Week 12 (V5), Week 26 (V6), Week 40 (V7), and Week 52 (V8). Visits 3, 4 and 5 should occur within ± 3 days of the scheduled time point. Visits 6 and 7 should occur within ± 7 days of the scheduled time point.

Details for the data collected at each visit are given in the time and events table in Section 11.2.

The revised design is shown in Figure 1 below. For reference, the original design is shown in Section 11.1.

Figure 1: Study Schematic Diagram



S – Screening R- randomization

1.2 Database Lock

The end of the study is defined as the date of the last safety follow up via phone call of the last participant in the study.

A Blind Data Review Meeting (BDRM) will take place prior to Database Lock (DBL) and Analysis Sets will be agreed.

1.3 Study Populations

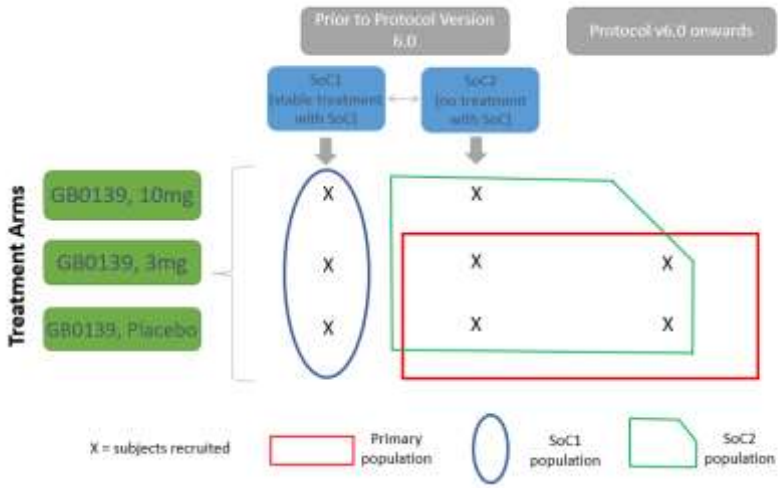
There are 3 populations of interest. These are as follows:

- **Primary Population** : Subjects recruited under the new design, plus those from the original design recruited to SoC2 (not being treated with nintedanib or pirfenidone prior to screening) and randomized to either placebo or 3mg GB0139.
- **SoC1 Population/Combination**: Subjects recruited under the original design to SoC1 (current treatment at baseline with nintedanib or pirfenidone).
- **SoC2 Population/Monotherapy**: Those subjects from the original design in the SoC2 stratum (not receiving nintedanib or pirfenidone at baseline), plus all subjects from

the new design. SOC2/Monotherapy Population is the Primary Population plus SoC2 10 mg.

These populations are described visually in Figure 2 below.

Figure 2: Populations for analysis



Randomized treatment and randomization strata will be identified per the randomization schedule post-unblinding.

Unless otherwise stated, all analyses will be conducted in the Primary Population. Analysis will be repeated in the SoC1 / Combination and / or SoC2 / Monotherapy Population where specified. For the SoC1 / Combination and SoC2 / Monotherapy Populations, there is an additional treatment arm and therefore an extra column will be displayed in the corresponding outputs.

A summary table showing the composition of the three populations by population, part and treatment group will be provided.

For further details on selection of subjects for analysis, see Section 4, Analysis Sets.

2. STUDY OBJECTIVES AND OUTCOME MEASURES

Primary and key secondary endpoints that refer to the 52 week timepoint will also be analyzed at the 26 week timepoint for the SoC1 /Combination and SoC2 / Monotherapy Populations.

2.1 Primary Efficacy Objective and Outcome Measures

Primary Efficacy Objective:	Primary Outcome Measures:
To evaluate the effect of GB0139 dry powder for inhalation compared with placebo over 52 weeks treatment period on the annual rate of decline in FVC in participants with IPF who are not treated with or cannot tolerate nintedanib or pirfenidone.	The annual rate of decline in Forced Vital Capacity (FVC; expressed in mL over 52 weeks) in those receiving 3mg or placebo and who are not being treated with nintedanib or pirfenidone.

2.2 Secondary Objectives and Outcome Measures

Secondary Efficacy Objective:	Key Secondary Outcome Measure:
To further characterize the effect of GB0139 compared with placebo over 52 weeks treatment period on FVC, quality of life, time to respiratory-related hospitalizations and all-cause mortality.	Proportion of subjects with an absolute decline from baseline in FVC (% pred) of ≤10% at Week 52. Change from baseline in St George's Respiratory Questionnaire (SGRQ) total score at Week 52. Time to first hospitalization (respiratory related, including acute exacerbation of IPF). Time to death (all causes).
	Other secondary outcome measures: Proportion of subjects with an absolute decline from baseline in FVC (% pred) of <=5% at week 52. Change from baseline in 6-minute walk test (6MWT) distance over 52 weeks. Change from baseline in diffusion capacity of the lung for carbon monoxide (DLCO), corrected for HB, over 52 weeks. Change from baseline at week 52 for dyspnea assessment by University of

	California San Diego - Shortness of Breath Questionnaire (UCSD - SOBQ). Change from baseline at week 52 for HRQoL as assessed by Short Form Survey (SF-36). Percentage of subjects with Adverse Events (AE) or Serious Adverse Events (SAE). Time to first hospitalization (IPF related, including acute exacerbation of IPF). Time to first hospitalization (all cause). Time to respiratory-related death. Change in FVC expressed in mL over 52 weeks for subjects who have never been treated with pirfenidone or nintedanib. [a]

[a] Only to be considered for the Primary and the SoC2 / Monotherapy Population.

2.3 Exploratory Outcome Measures

- Change from baseline in selected biomarkers including but not limited to: YKL 40, PAI1, PDGF-BB, MCP-1, CCL-18, KL-6, CA-125, CA-19, Gal-3, MMP7 and collagen neoepitopes over time up to week 52 in all subjects.

- Time to initiation of pirfenidone or nintedanib treatment for SoC2 / Monotherapy subjects recruited to the original study design (prior to Protocol V6.0).

- Time to termination of pirfenidone or nintedanib treatment [b].

- Analysis of GAL-3 and IPF disease related genes of interest that might relate to the efficacy and/or safety of GB0139.

[b] Only for the SoC1 /Combination Population.

2.4 Safety

The following measures of safety will be assessed throughout the study:

- Vital signs
- Physical examination
- Weight
- Clinical laboratory tests (haematology and clinical chemistry)
- Adverse events
- 12-lead electrocardiogram (ECG)

3. STUDY DESIGN

Full details of the study design can be found in the CSP Section 6.

3.1 Sample Size Determination

In the original design, the planned 150 subjects per arm (randomized 1:1:1 to the 3 treatment arms) provided approximately 87% power to detect a true mean difference of 100 ml between treatment arms in the FVC decline at Week 52, assuming a between subject standard deviation of 280ml, based on a two-sided 5% significance level.

For the updated design, the randomization ratio was changed to 2:1 (GB0139 3mg: Placebo). To detect a difference from placebo in the decline of FVC of 100ml with a standard deviation of 240ml at the significance level of 10%, a sample size of 141 would give 75% power. The lower standard deviation in the updated design was based on a blinded review of the data.

3.2 Randomization and Blinding

In the original design, within each SoC subpopulation (SoC1: subjects on nintedanib/pirfenidone at baseline, SoC2: subjects not treated with nintedanib/pirfenidone), subjects were randomized in blocks to double-blind treatment in a 1:1:1 ratio (GB0139 3 mg: GB0139 10 mg: Placebo).

For the updated design, there is no stratification and subjects are randomized in a 2:1 ratio GB0139 3mg: Placebo. The unbalanced randomization is to maintain the same probability of allocation to placebo post design change, since it is considered that this may facilitate participant enrollment.

The Sponsor arranged for the randomization and the packaging and labelling of trial medication. The randomization list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both

reproducible and non-predictable. The block size will be documented in the Clinical Study Report (CSR). Access to the codes will be controlled and documented.

This study is a double-blind study which will be maintained throughout the study, including the follow up period. The only exception to this is at the point of the design change, when the 10mg group in the SoC2 stratum had to be unblinded in order to withdraw them from the study early. Study medication is identified by a medication code number. Packaging and labelling will be otherwise identical. An Integrated Web Response System (IWRS) will be used to assign subjects to treatment groups at study start. The randomization code will be kept undisclosed up to database lock.

Other than designated unblinded team members at Syneos Health to support DSMB review, all subjects, Investigators and everyone involved in analyzing or with an interest in this double- blind study (Sites, Study team, Plus-Project, other service providers) will remain blinded to the randomized treatment assignments from both the original and the updated design until after database lock. A team from Syneos Health Biostatistics will have access to unblinded information to perform analyses for the DSMB (using controlled restricted folder access). DSMB members will receive outputs using coded treatments, so that summaries are separated by treatment, but it cannot be deduced which treatment code represents which treatment. The DSMB will have the option to request direct unblinding information at any point in line with the DSMB charter.

4. ANALYSIS SETS

In accordance with International Conference on Harmonisation (ICH) E3 [3] and E9 [4] guidelines, the analysis sets are defined as follows:

4.1 Screened Set

The Screened Set will include all subjects who provide informed consent for the study. This set will be used for subject listings and summaries of subject disposition.

4.2 Intention-to-treat (ITT) Set

All randomized subjects regardless of treatment received. Subjects will be analyzed based on the treatment to which they were randomized. The ITT set will be used for presentation of subjects in listings of demographic data and efficacy data.

4.3 Modified ITT (mITT) Set

This will comprise all randomized subjects who have had at least one dose of trial medication. Again, the subjects in this set will be analyzed according to the treatment to which they were randomized. The mITT set will be used for analysis of efficacy and biomarker endpoints and will be the primary analysis set of the study used for the primary and key secondary endpoints.

4.4 Safety Analysis Set (SS)

All subjects who have had at least one dose of trial treatment will be analyzed for safety.

For all safety summaries, subjects with at least one dose of GB0139 or Placebo will be analyzed according to the first study treatment they received.

4.5 Per Protocol Set (PPS)

The PPS is a subset of the mITT set consisting of subjects who complied with the protocol sufficiently to ensure that these data would be likely to represent the effects of study intervention according to the underlying scientific model (e.g., subjects with at least 80% treatment compliance as defined in Section 7.3.1). It is used for efficacy sensitivity analyses and will only apply to the Primary Population.

It consists of all randomized and dosed subjects who meet key inclusion/exclusion criteria, only received the treatment they were randomized to, and did not have protocol deviations that were considered to impact efficacy. Subjects recruited under the original study design and who started nintedanib or pirfenidone whilst still on randomized treatment and prior to 52 weeks (i.e., in combination with study treatment) will be excluded from the PP Set. The following list of criteria will be used to exclude subjects from the Primary Population:-

- Not in Primary Population
- HRCT not done
- Treatment compliance not 80-120%
- FVC (%pred) <=45% at Baseline
- DLCO (corrected for Hb) <30% or >79% of predicted at Baseline
- FEV1/FVC <0.7 at Baseline
- Use of nintedanib or pirfenidone during study

The final classification of protocol deviations relative to Week 52 will be made during a blinded data review prior to DBL, and all decisions, including exclusions from the PP Analysis Set, will be made blinded to study treatment.

4.6 Protocol Deviations and Blind Data Review Meeting

Protocol Deviations and Non-Compliances will be handled and reviewed regularly during the study according to a study specific 'Protocol Deviation and Non-compliance Management Plan' created in line with Syneos Health controlled document 'Processing and Management of Protocol Deviations (3101.W02)'. All Protocol Deviations and Non-Compliances will be consolidated into one workbook outside of the eCRF for regular review of each entry in terms of its classification of Minor or Major and any effect on efficacy.

Shortly prior to database lock and unblinding of subject's treatment assignment, a BDRM will take place to adjudicate SAP definitions, protocol deviations and any other non-compliances, and agree on exclusions from the PP Set. Additionally, any further actions related to the database, SAP and/or Protocol Deviations and Non-Compliances workbook may be discussed and actioned. Decisions and actions agreed at the BDRM (including any follow-up notes) will be documented.

The strategy for the presentation of results by the 'treatment received group' will be discussed and agreed at the BDRM.

5. GENERAL METHODS AND PRINCIPLES

The SAP will be finalized and signed-off prior to DBL and unblinding. Any post-hoc analysis (analyses performed post DBL that are different from those described in the final version of the SAP) will be documented in the final clinical study report (CSR) as changes to the planned analysis.

All data collected will be listed, sorted by strata/treatment group, Subject ID, visit and time, with the Primary Population listed first as follows:-

- SoC2/Monotherapy Placebo,
- SoC2/Monotherapy GB0139 3 mg,
- SoC2/Monotherapy GB0139 10mg,
- SoC1/Combination Placebo,
- SoC1/Combination GB0139 3 mg,
- SoC1/Combination GB0139 10mg,
- Screening Failures.

Data on screening failures will be listed only.

Tabulations and data analyses will be performed using SAS® software, version 9.4 or later (SAS Institute, Inc.).

Unless otherwise specified, efficacy analyses will be performed in the mITT Analysis Set, with sensitivity analyses of the primary endpoints and secondary endpoints conducted using the PPS. Safety summaries will be performed using the SS Analysis Set. The ITT Analysis Set will be used to describe demographics, baseline characteristics and medical history.

The populations will be split according to SOC1 / Monotherapy and SOC2 / Combination, as well as per treatment group.

P-values will be generated for all efficacy treatment comparisons, in all populations, as an exploratory tool for detection of potential contrasts in the material. P-values will not be generated for subgroup analyses.

5.1 Standard Descriptive Statistics

Continuous variables

Unless specified otherwise, the following standard descriptive statistics by treatment group will be obtained for continuous variables: number of subjects with non-missing values, mean, standard deviation, median, 25th percentile, 75th percentile, minimum and maximum value.

Categorical variables

Unless specified otherwise, the following standard descriptive statistics by treatment group will be presented for categorical values: total number, number of values in each category and the corresponding percentage of the total number of non-missing values will be calculated.

5.2 Definition of Analysis Visits

Assessments will be mapped to analysis visits for a variable as follows:

- Find the closest non-missing, within time-window (as per Table 1 below) result taken to the scheduled day as per the protocol schedule of assessments.
- If two assessments are equal distance either side of the scheduled day, then take the earlier result.

Table 1: Study visits and analysis visit windows

Visit	Description	Scheduled Day	Analysis window, Primary Population	Analysis window, SoC1 / Combination and SoC2 / Monotherapy Populations	Analysis Visit
V2	Baseline / Randomization	1	n/a	n/a	Baseline
V3	Visit 3 / Week 4	29	2-43	2-43	Week 4
V4	Visit 4 / Week 8	57	44-71	44-71	Week 8
V5	Visit 5 / Week 12	85	72-134	72-134	Week 12
V6	Visit 6 / Week 26	183	135-232	135-232	Week 26
V7	Visit 7 / Week 40	281	233-323	233-323	Week 40
V8 [a]	Visit 8 / Week 52	365	324-453	324-453	Week 52
V8 [b]	Visit 8 / Week 52	365	>=324	324-453	Week 52
FUV1 [a]	Follow-up 1 / Week 76	541	454-635	454-635	Week 76
FUV2 [a]	Follow-up 2 / Week 104	728	>=636	>=636	Week 104

[a] Subjects recruited under original design only.
[b] Subjects recruited under the updated design only.
Note: For the updated design, at the Follow up visit 7 days after the final study day visit only adverse events and concomitant medications are collected (does not require analysis visit windows).

All efficacy data will be considered for efficacy summary tables (i.e. summary tables by visit will include Week 76 and Week 104) but all data post Day 453 will be omitted from the efficacy analysis tables and any efficacy figures presented by visit will only be up to Week 52.

For time to event endpoints, Day 379 (Week 52 plus 2 weeks) will be considered the end of the period under consideration.

All safety data collected will be included in summaries.

In the proceeding sections of this SAP visit will mean analysis visit assignment per Table 1 unless stated otherwise.

5.3 Description of Baseline

For all treatment groups and under both designs, the baseline is defined as the last available, non-missing, value before or on Study Day 1. Study Day 1 is defined as the day of dosing (or the day of randomization for subjects randomized and not dosed).

At Week X, absolute change from baseline will be defined as value at Week X – baseline value.

5.4 Tables, Listings and Figures Presentation

All outputs will be incorporated into PDF files, sorted and labelled according to the ICH recommendations, and formatted to the appropriate page size(s).

For all outputs, the order and labels of the treatment groups will be displayed as per Table 2 below:

Table 2: Ordering and labelling of treatment groups for each population

Primary Population	SoC1 / Combination Population	SoC2 / Monotherapy Population
Placebo GB0139 3mg Total *	Placebo GB0139 3mg GB0139 10mg Total*	Placebo GB0139 3mg GB0139 10mg Total*

*Where applicable.

Table 3 shows the study visit labels to be used in the listings.

Table 3: Study visit labels

Visit Number (Title)	Visit Label
Visit 1 (Screening)	Screening
Visit 2 (Baseline / Randomization)	Baseline
Visit 3 (Week 4)	Week 4
Visit 4 (Week 8)	Week 8
Visit 5 (Week 12)	Week 12
Visit 6 (Week 26)	Week 26
Visit 7 (Week 40)	Week 40
Visit 8 (Week 52)	Week 52
Follow-up Visit 1 (Week 76) [a]	Week 76 (FUV1)
Follow-up Visit 2 (Week 104) [a]	Week 104 (FUV2)
Follow up telephone call [b]	Follow-up call
Unscheduled	Unscheduled

[a] Applicable to subjects in the SoC1 / Combination and SoC2 / Monotherapy Populations only

[b] Applicable to subjects in the Primary Population only

The listings will display all the data contained in the EDC system. All screen failure information will be listed separately. The listings will be ordered by strata, treatment group, site, subject, visit and visit date unless otherwise stated. All AE listings will contain age, sex, weight and race.

Summaries for continuous variables will use the descriptive statistics as described in Section 5.1. The number of decimal places to be displayed for each will be as follows:

- Mean, median, 25th percentile and 75th percentile: one more decimal place than source data.
- Standard deviation, coefficient of variation: two more decimal places than data.
- Minimum and maximum: same number of decimal places as data.
- Confidence intervals: 2 decimal places.
- P-value: 3 decimal places, if less than 0.001 then display as “<0.001“.

Categorical variables will be presented as frequency counts and percentages. Percentages will be displayed to one decimal place throughout in the Tables, Figures and Listings (TFLs). If the count is 0, the percentage will not be displayed.

All dates will be displayed in the format DDMONYYYY.

Calculations using dates will follow these conventions:

- The relative study day of the event (DAY) is calculated as the difference between the date of the event of interest (EVENT DATE) and reference start date, where reference start date is defined as the date of first dose of study medication for all subjects, i.e.

DAY = EVENT DATE – REFERENCE START DATE + 1 for EVENT DATE ≥ REFERENCE DATE
DAY = EVENT DATE – REFERENCE START DATE for EVENT DATE < REFERENCE DATE

- Durations will be calculated by: DURATION = (STOP DATE – START DATE) + 1

6. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

6.1 Subject Disposition

Subject disposition data will be presented by randomized treatment group.

The following will be summarized for each of the populations based on the ITT Analysis Set unless otherwise stated:

- Subjects screened, screen failed (including reasons), randomized, randomized after re-screening, randomized and not dosed, and dosed (Screened Set). For this output only, a total column will also be included.
- Treatment completion (including reasons for discontinuation).
- Study completion (including reasons for discontinuation).
- Major protocol deviations will be summarized by category and whether they lead to exclusion from the PP Set.
- Analysis sets (including reasons for exclusion).

Specific details related to study treatment discontinuation and study discontinuation captured as free text fields in the CRF will be listed only.

Supportive listings will be provided for all subjects (including screen failures); date of informed consent, date of informed re-consent, randomization (yes/no), date of randomization and, where available, reasons for non-randomization will be included.

Violation of inclusion/exclusion criteria will be listed.

6.2 Demography and Baseline Characteristics

The following demographic and baseline characteristic variables will be summarized (with unit for continuous variables or categories for categorical variables) for the ITT, mITT and PP Sets:

- Age (complete years) from eCRF
- Age group (<70 years / >= 70 years)
- Gender (Male/ Female)
- Race (American Indian or Alaska Native/ Asian/ Black or African American/ Native Hawaiian or Other Pacific Islander/ White/ Other)
- Ethnicity (Hispanic or Latino/ Not Hispanic or Latino)
- Country (Australia/ Belgium/ Canada/ France/ Georgia/ Germany/ Ireland/ Israel/ Italy/ Poland/ Russia/ Spain/ Ukraine/ United Kingdom/ United States). This will be derived from the country code in the subject number.
- Height (cm)
- Weight (kg)
- Body Mass Index (kg/m^2) [derived in the eCRF]
- Smoking Status (Current-smoker/ Ex-smoker/ Never smoked)
- Diagnosis Confirmed from HRCT for Fleischner criteria (Yes/ No)
- Pirfenidone or Nintedanib Usage at Screening (Current/ Previous/ Never)
- SoC Randomized Strata (SoC1 / SoC2) – per randomization
- Forced Vital Capacity (mL)
- 6-Minute Walk Test Total Distance (m)
- DLCO corrected for HB (mmol/min/kPa)
- UCSD – SOBQ Total Score
- SF-36 Total Score
- SGRQ Total Score
- Serum galectin-3 at baseline

Medical History (split by prior / ongoing) and Prior / Concomitant Medications will be described by frequency tables for the Safety Set.

The number of subjects randomized at each country and site will be summarized by treatment group for the ITT.

All summaries (other than those in the PP Set) will be repeated for the SoC1 /Combination and SoC2 / Monotherapy populations and supportive listings will be provided.

6.3 Prior and Concomitant Medication (excluding pirfenidone and nintedanib)

Data relating to medications other than pirfenidone or nintedanib will be presented according to data collected in the 'Prior and Concomitant Medications' page of the eCRF and will be coded using the most recent upversioned World Health Organization (WHO) Drug Dictionary as specified in the Data Management Plan (DMP).

Each medication will be assessed for whether it was prior medication, concomitant medication or medication taken post-treatment.

For partial/missing dates, the following approach will be taken:

- Prior medication: If the stop month/year (if day is missing) or year (if day and month are missing) of the medication is prior to the respective month/year or year of the first dose of study drug then the medication will be classed as prior.
- Medications taken post-treatment: If the start month/year (if day is missing) or year (if day and month are missing) of the medication is after the respective month/year or year of the date of discontinuation of study drug then the medication will be classed as taken during follow-up.
- Otherwise, the medication will be concomitant.

Subject incidence of prior and concomitant medication (excluding pirfenidone and nintedanib usage (separate summaries)) will be summarized for the Safety Analysis Set by Anatomic Therapeutic Class (ATC) 1, ATC 3 and preferred name as well as overall. Summaries will be presented by ATC 1, ATC 3 and preferred name, sorted by decreasing frequency over all subjects and then alphabetically. Subjects will be counted only once for each ATC code or preferred name, if they have multiple records of the same ATC codes or preferred name in the database.

Summaries will be repeated for both the SoC1 / Combination and SoC2 / Monotherapy Populations and a listing will be provided. Medications taken post-treatment will be listed only.

6.4 Previous use of Pirfenidone and Nintedanib

Previous use of pirfenidone and nintedanib will be recorded in the 'Pirfenidone/Nintedanib Usage' page of the CRF and will be summarized separately to other previous medications. Duration of treatment (up to date of randomization, for those on pirfenidone or nintedanib at baseline), time since end of treatment (where applicable) and reasons for discontinuation will be summarized.

Summaries will be repeated for both the SoC1 / Combination and SoC2 / Monotherapy populations, and a supportive listing will be provided.

6.5 Prior and Concomitant Procedures

Data related to concurrent and post-treatment surgery or procedures in the 'Surgery and Procedure' eCRF will be coded using most recent up-versioned MedDRA coding as specified in the DMP.

The same definitions of concomitant and post-treatment will be applied as for medications (see Section 6.3).

Subject incidence of concurrent and follow-up surgery or procedures will be summarized separately, presented overall and by System Organ Class (SOC) and preferred term (PT). Within each separate summary, subjects will be counted only once for each SOC or PT if they have multiple records of the same SOC or PT term in the database.

7. STATISTICAL METHODS AND PRINCIPLES

This section describes the statistical analyses, presentation of the results, and the study endpoints that will be collected and/or derived during the study at the time points specified in the Schedule of Events (see Appendix 2 (Section 11.2)).

7.1 General Methods and Principles

7.1.1 Analysis of Subgroups

Key subgroups for the study are:-

- Baseline FVC (%PRED): <80%, >=80%
- GAP index: I, II or higher
- Baseline GAL-3 level: < median, >= median*
- Baseline MMP7: < median, >= median
- Gender (Female, Male)
- SoC treatment at baseline per eCRF (pirfenidone, nintedanib) for SoC1 / Combination Population only. Any SoC1 subject per the randomization who did not receive pirfenidone/nintedanib per the eCRF will be omitted from these subgroup analyses**

* Median baseline GAL-3 levels will be estimated per SoC population separately.
** Only to be used for FVC (primary endpoint) and treatment compliance.

Other subgroups may be analyzed on inspection of the data.

7.1.2 Methods for Handling Missing Values

In general, missing data will not be imputed. Exceptions are detailed in the subsequent sections.

7.1.3 Multiplicity

No adjustments for multiplicity are to be made in this study.

7.1.4 Pooling of Sites

No pooling of sites will be performed in this study.

7.2 Efficacy

All efficacy data described below will be summarized by visit including the change from baseline (when applicable).

7.2.1 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is the annual rate of decline in Forced Vital Capacity (FVC; expressed in mL over 52 weeks). Spirometry data provided by an external vendor showing the FVC (L) will be multiplied by 1000 to convert to mL. The analyses will be based on all FVC values obtained. Any FVC values post Day 453 will be omitted from the analyses.

The primary efficacy endpoint will be analyzed according to the estimand framework. Strategies for handling FVC data affected by the inter-current events (ICEs) of death, treatment discontinuation, and initiation of additional IPF therapy (pirfenidone or nintedanib) will be employed. Full details regarding use and imputation of FVC data in relation to ICEs are given in the next section.

7.2.2 Main Estimand and Analysis

The primary analysis will test for superiority of GB0139 3mg compared to Placebo (Plc) for the annual rate of decline in FVC in mL over 52 weeks in subjects not receiving pirfenidone or nintedanib at baseline in the mITT Set. The main estimand for the primary efficacy endpoint is as follows:

- Population: Primary Population, mITT set.
- Variable of interest: Change from baseline in FVC in mL over 52 weeks
- Intercurrent events:
    - Death: FVC attributed the lowest value recorded in the trial when a patient dies

- Treatment Discontinuation: Analysis will include any FVC measurements after randomised treatment discontinuation
- Initiation of additional IPF therapy (nintedanib or pirfenidone): Analysis will include any FVC measurements after initiation of additional IPF therapy

- Summary measure: Comparison of slopes assessed through the treatment by time interaction.

The null hypothesis is:

H_0: There is no difference in the annual rate of decline in FVC in mL between GB0139 3mg and Plc

The alternative hypothesis is:

H_a : There is a difference in the annual rate of decline in FVC in mL between GB0139 3mg and Plc

A restricted maximum likelihood (REML) approach will be used, with a random coefficient regression (random slopes and intercepts) model fitted to test the hypotheses. The decrease in FVC is assumed to be linear within each subject over 52 weeks [5].

Baseline FVC and time will be fitted as continuous covariates. The treatment group and the interaction term for time by treatment group will be added as fixed effects. Random subject intercept and time effects will be fitted and will be assumed to be normally distributed with arbitrary covariance matrix. The within-subject errors will be assumed to be independent and normally distributed with mean zero and a common variance. The Kenward-Roger approximation will be used to estimate denominators degrees of freedom.

The statistical model will be as follows:

$$Y_{itk} = (\alpha + a_i + \tau_k) + \beta_f FVCb_i + (\gamma + \beta_3 T_3 + g_i)\, t + \varepsilon_{it}$$

where:

Y_{itk} is the change from baseline measured for ith patient at time t (actual time) in treatment group k

t is the time since randomization in years

T_3 =1 if the subject is in the GB0139 3mg group, otherwise T_3 =0

β_3 is the effect of treatment on the slope compared to Placebo

α and γ are elements of the intercept and slope respectively

a_i and g_i are random specific components of the intercept and slope respectively for the ith patient, assumed to be normally distributed with mean 0 and arbitrary covariance matrix

$FVCb_i$ is the baseline FVC (mL) for the ith patient

τ_k is the intercept coefficient of the effect of treatment k (k=1, 2)

β_f is the effect of 1ml increase in the baseline FVC

ε_{it} is the random error for ith patient at time t assumed to be independent and normally distributed with mean 0 and variance σ^2

This approach adopts a missing at random (MAR) assumption (i.e., the probability of an observation being missing depends only on observed measurements). Subjects with missing data at a particular time point still contribute to the analysis at that time point based on their other observed data used in the model (i.e., treatment, baseline FVC, and the FVC at baseline). Data that remain unobserved due to ICEs will be handled as described above. Other missing data will be imputed within the regression model under the MAR assumption.

The linearity assumption for the rate of change in FVC from baseline to week 52 will be explored graphically. Graphical displays will be provided of the mean (± SEM) observed FVC and mean change from baseline for each treatment group by visit.

The assumptions of the analysis will be checked by inspection of graphical displays of the residuals.

A cumulative distribution plot of the percentage of subjects by change from baseline in FVC in mL at week 52 will be presented.

The primary analysis detailed above will be repeated for the Primary Population, PP Analysis Set and for SoC1 / Combination and SoC2 / Monotherapy Populations (only for the mITT Analysis Set).

7.2.2.1 Primary Endpoint Supporting Analyses

Supporting analyses will be carried out in the SoC1 / Combination and SoC2 / Monotherapy Populations. The estimands for these analyses differ from the primary estimand of Section 7.2.1 only in the population and the variable of interest.

In all supporting analyses, the variable of interest, in addition to the change from baseline in FVC over 52 weeks, is the change from baseline in FVC in mL over 26 weeks. Any FVC values post Day 232 will be omitted from these analyses. The estimated rate of decline in FVC in mL will be produced based on 26 weeks of data. This analysis will also be repeated for the Primary Population.

Separate analyses will be performed for each of the SoC1/ Combination and SoC2 / Monotherapy Populations in the mITT Set.

All statistical analyses and graphical summaries will be as described in Section 7.2.1.

7.2.2.2 Subgroup Analysis

The primary analysis detailed in Section 7.2.1 will also be repeated by subgroup (separately for each subgroup factor of interest) for the Primary Population (52 week and 26 week endpoint) and the SoC1 / Combination Population (52 week and 26 week endpoint) in the mITT Set. The time by treatment group interaction will be replaced with a time by treatment group by subgroup interaction and fixed effect for the subgroup factor will also be added. The effect on slope between treatments will be assessed within each level of the subgroup.

7.2.2.3 Supplementary Analysis

Supplementary analyses of the primary efficacy endpoint in the Primary Population will be performed as follows:

		Handling of intercurrent events		
Supple-mentary Analysis	Analysis Set	Death	Treatment discontinuation	Initiation of additional IPF therapy
1	mITT Set, Primary Population	FVC attributed lowest value recorded in the trial when a patient dies	Analysis will exclude all available FVC measurements after randomized treatment discontinuation	Analysis will exclude all available FVC measurements after initiation of additional IPF therapy
2	mITT Set, Primary Population	FVC attributed 0 when a patient dies	Analysis will include all available FVC measurements after randomized treatment discontinuation	Analysis will include all available FVC measurements after initiation of additional IPF therapy

7.2.2.4 Primary Estimand Sensitivity Analysis

A Mixed Model with Repeated Measures (MMRM) will be fitted to the change from baseline in FVC across all visits with data imputed at Week 52 per the primary estimand (i.e. Week 52 will be attributed the lowest value recorded in the trial when a patient dies). Treatment, visit, baseline FVC, and treatment-by-visit interaction will be fitted as fixed effects. A restricted maximum likelihood (REML) approach will be used, and an unstructured covariance structure shared across treatment groups will be used to model the within-subject errors. If the model fails to converge, a heterogeneous Toeplitz structure (TYPE=TOEPH option in PROC MIXED rather than TYPE=UN) will be used. The Kenward-Roger's correction to degrees of freedom will be applied.

If there are concerns regarding the amount of missing data for the primary estimand, a sensitivity analysis to test the robustness of the MAR assumption used in the main estimand analysis will be performed to assess the results with missing Week 52 FVC data. A multiple imputation approach will be used. Full details of the methods to be followed are given in Section 11.4 and 11.5.

7.2.3 Key Secondary Efficacy Endpoints Analysis

For all key secondary endpoints, analyses will be performed in the Primary Population and in the SoC1 / Combination and SoC2 / Monotherapy Populations. As described previously, for the SoC1 / Combination and SoC2 / Monotherapy Populations, endpoints that refer to 52 weeks will in addition consider the 26 week timepoint (where applicable). Subgroup analyses will only be performed for the Primary Population and the SoC1 / Combination Population.

Initial analyses and subgroup analyses will be performed in only the mITT Analysis Set . Kaplan-Meier plots (where applicable) will only be produced for the mITT Set.

7.2.3.1 Proportion of subjects with an absolute decline from baseline in % Predicted FVC of ≤10% at Week 52

Spirometry data provided by an external central vendor (Clario/ERT) showing the calculated % Predicted FVC will be used to derive whether the subject showed an absolute decline ≤10% from baseline in predicted %FVC at Week 52.

The superiority of GB0139 3mg compared to Placebo will be tested for the proportion of subjects with an absolute decline ≤10% from baseline in predicted %FVC at week 52.

The null hypothesis is:

H_0: There is no difference in the proportion of subjects with an absolute decline ≤10% from baseline in predicted %FVC between GB0139 3mg and Plc.

The alternative hypothesis is:

H_a: There is a difference in the proportion of subjects with an absolute decline ≤10% from baseline in predicted %FVC between GB0139 3mg and Plc.

A logistic regression model will be fitted with treatment and baseline FVC (mL) included in the model. The Wald test will be used to test for differences between treatments. Odds ratios together with 90% and 95% confidence intervals will be used to quantify the effect of treatment, comparing GB0139 3mg to Placebo as the reference.

Subjects lost to follow-up prior to Week 52 are imputed to have absolute decline >10% from baseline in predicted %FVC at Week 52.

The analysis will be repeated by subgroup (separately for each subgroup factor of interest, Section 7.1.1) by adding a fixed effect for the subgroup factor and adding a treatment by subgroup interaction term. The odds ratio between treatments will be assessed within each level of the subgroup.

Graphical displays will be provided of the mean (± SEM) observed predicted %FVC and mean change from baseline for each treatment group by visit.

7.2.3.2 Change from baseline in St. George's Respiratory Questionnaire total score at Week 52.

Data from an external central vendor (Clario/ERT) with the SGRQ results will be used. The details of scoring are provided in Section 11.6.

A Mixed Model with Repeated Measures (MMRM) will be fitted to the change from baseline in the SGRQ Total Score across all visits (Weeks 12, 26 and 52 - see Section 11.2). Treatment, visit, baseline SGRQ Total Score, and treatment-by-visit interaction will be fitted as fixed effects. A restricted maximum likelihood (REML) approach will be used, and an unstructured covariance structure shared across treatment groups will be used to model the within-subject errors. If the model fails to converge, a heterogeneous Toeplitz structure (TYPE=TOEPH option in PROC MIXED rather than TYPE=UN) will be used. The Kenward-Roger's correction to degrees of freedom will be applied.

Domain scores will be summarized by treatment group and visit only.

The analysis will be repeated by subgroup (separately for each subgroup factor of interest). A fixed effect for the subgroup factor will be added and all interaction terms between treatment, visit and the subgroup factor will be included. The comparisons between treatments at each visit will be assessed within each level of the subgroup.

7.2.3.3 Time to first hospitalization (respiratory related, including acute exacerbation of IPF)

The time to first hospitalization (respiratory related, including acute exacerbation of IPF) will be derived from the 'Exacerbation' and 'Adverse Events' eCRF.

If the subject was hospitalized and the AE linking to the hospitalization indicates that the PI/treating physician classed the AE as the result of an exacerbation of IPF then the hospitalization will be defined as being respiratory related, including acute exacerbation of IPF.

Other respiratory related causes will be defined as all AEs in the 'Respiratory, Thoracic and Mediastinal Disorders' System Organ Class (SOC), plus those AEs in the 'Infections and Infestations' SOC with preferred terms containing the character strings 'resp', 'bronch', 'covid-19' or 'pneumo', or the specific PTs as follows:

- Influenza
- Legionella infection
- Viral infection

If a subject was hospitalized (respiratory related, including acute exacerbation of IPF) prior to or on Day 379 (Week 52 plus 2 weeks) then the (date of first such hospitalization – date of randomization +1)/7 will be derived as the time to first hospitalization (respiratory related, including acute exacerbation of IPF) in weeks.

If a subject does not require hospitalization (respiratory related, including acute exacerbation of IPF) prior to or on Day 379, they will be censored in the analysis. The following censoring rules will be applied:-

- If lost to follow-up (LTFU), a subject will be censored at the earliest of date of last contact and Day 379
- If a subject discontinued (and not lost to follow-up), they will be censored at the earlier of the date of study discontinuation and Day 379.
- Otherwise, censor at the earliest of last contact date or Day 379.

The superiority of GB0139 3mg compared to Placebo will be tested for the time to first hospitalization (respiratory related, including acute exacerbation of IPF).

The null hypothesis is:

H_0 : There is no difference in the time to first hospitalization between GB0139 3mg and Plc

The alternative hypothesis is:

H_a: There is a difference in the time to first hospitalization between GB0139 3mg and Plc

A Cox proportional hazards model will be fitted with treatment and baseline FVC (mL) included in the model. The Wald test will be used to test for differences between treatments. Hazard ratios together with 90% and 95% confidence intervals will be used to quantify the effect of treatment, comparing GB0139 3mg to Placebo as the reference. Breslow's method for handling ties will be used.

The analysis will be repeated by subgroup (separately for each subgroup factor of interest) by adding a fixed effect for the subgroup factor and adding a treatment by subgroup interaction term. The hazard ratio between treatments will be assessed within each level of the subgroup.

If there are fewer than 15 events (respiratory related, including acute exacerbation of IPF) then a formal statistical analysis will not be performed, and only frequencies of hospitalizations by treatment group will be provided. If an overall analysis is performed, then the subgroup analyses will automatically be performed, regardless of the number of events in the subgroup levels.

Kaplan-Meier plots by treatment group will also be presented.

7.2.3.4 Time to death (from all causes)

If a patient dies on or prior to Day 379, the date of death will be obtained from the 'Disposition Study Completion' eCRF. The time to death in weeks will be derived as (date of death – date of randomization +1)/7 .

If a patient does not die on or prior to Day 379, the same censoring rules will apply as in Section 7.2.3.3.

The superiority of GB0139 3mg compared to Placebo for time to death from all causes from date of randomization will be tested, regardless of the number of events.

The null hypothesis is:

H_0: There is no difference in time to death for all causes between GB0139 3mg and Plc.

The alternative hypothesis is:

H_a: There is a difference in time to death for all causes between GB0139 3mg and Plc.

The same model will be used as described in Section 7.2.3.3.

7.2.4 Other Secondary Endpoint Analysis

Unless otherwise stated, all other secondary endpoints will be statistically analyzed only for the Primary Population. For the SoC1 / Combination and SoC2 / Monotherapy Populations, only descriptive summaries will be provided. All analyses will use the mITT set, unless otherwise specified.

No subgroup analyses will be performed for these endpoints.

7.2.4.1 Proportion of subjects with an absolute decline from baseline in % Predicted FVC of ≤ 5% at Week 52

The same data source and analyses (logistic regression) as detailed in Section 7.2.3.1 will be used.

7.2.4.2 Change from baseline in 6-minute walk test (6MWT) distance over 52 weeks

Data from an external vendor with the 6MWT results will be used. To compare the change from baseline in the distance covered in the 6MWT at Week 52, an Analysis of Covariance (ANCOVA) will be fitted with treatment and baseline 6MWT distance included in the model. The least squares means per treatment and difference in least square means between treatments and 90% and 95% CI will be presented.

Data collected at early withdrawal visit will be summarized descriptively only.

7.2.4.3 Change from baseline in diffusion capacity of the lung for carbon monoxide (DLCO), corrected for HB, at 52 weeks

Data from an external vendor with the DLCO result (mmol/min/kPa) will be used. The same analyses (ANCOVA) as detailed in Section 7.2.4.2 will be used but using the baseline DLCO rather than baseline 6MWT in the ANCOVA model.

Data collected at early withdrawal visit will be summarized descriptively only.

7.2.4.4 Change form baseline at week 52 in dyspnea assessment by University of California San Diego - Shortness of Breath Questionnaire (UCSD - SOBQ)

Data from an external vendor with the UCSD – SOBQ scores will be used. The UCSD – SOBQ comprises of 24 items scored 0-5 where (0 = "not at all" to 5 = "maximal or unable to do because of breathlessness"). The item scores will be summed (treating any missing as 5) to derive a total score between 0 and 120. The UCSD – SOBQ items are provided in Section 11.7. The same MMRM analysis as detailed in Section 7.2.3.2 will be used for the change from baseline at week 52 in UCSD – SOBQ Total Score, using the baseline UCSD – SOBQ Total Score rather than the baseline SGRQ Total Score.

7.2.4.5 Change from baseline at Week 52 for HRQoL as assessed by Short Form Survey (SF-36)

Data from an external vendor with the SF-36 scores will be used. The change from baseline in SF-36 total score will be analyzed using an MMRM the same as detailed in Section 7.2.3.2 using the corresponding baseline SF-36 total score rather than the baseline SGRQ total score.

In addition, the actual and change from baseline in individual component scores as follows will be summarized by treatment group and visit:

- Physical component scale (PCS) and mental component scale (MCS).
- Physical functioning (PF), role physical (RF), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH).

The details of scoring are provided in Section 11.8.

7.2.4.6 Percentage of subjects with Adverse Events (AE) or Serious Adverse Events (SAE) over 52 weeks

Only TEAEs with a start date prior to Day 379 will be considered for inclusion in the analysis. Summaries of the percentage of subjects with AE or SAEs will be presented for each population by SOC and PT. No formal analyses will be performed.

7.2.4.7 Time to first hospitalization (IPF related, including acute exacerbation of IPF)

The time to first hospitalization (IPF related, including acute exacerbation of IPF) will be derived from the ‘Exacerbation’ and ‘Adverse Events’ eCRF.

If the subject was hospitalized and the AE linking to the hospitalization indicates that the PI/treating physician classed the AE as the result of an exacerbation of IPF then the hospitalization will be defined as being IPF related, including acute exacerbation of IPF.

The time to first hospitalization (IPF related, including acute exacerbation of IPF) in weeks will be derived as (date of first such hospitalization – date of randomization +1)/7.

If a patient does not require hospitalization (IPF related, including acute exacerbation of IPF) on or prior to Day 379, the same censoring rules will apply as in Section 7.2.3.3.

If there are fewer than 15 hospitalizations (IPF related, including acute exacerbation of IPF) then statistical analysis will not be performed, and only frequencies of hospitalizations by treatment group will be provided. Otherwise, the same analysis (Cox proportional hazards modelling) as detailed in Section 7.2.3.3 will be performed.

7.2.4.8 Time to first hospitalization (all cause)

If the subject was hospitalized, then the hospitalization will be defined as all cause. The time to first hospitalization (all cause) in weeks will be derived as (date of first hospitalization – date of randomization +1)/7.

If a patient does not require hospitalization on or prior to Day 379, the same censoring rules will apply as in Section 7.2.3.3.

If there are fewer than 15 hospitalizations (all cause) then statistical analysis will not be performed, and only frequencies of hospitalizations by treatment group will be provided. Otherwise, the same analysis (Cox proportional hazards modelling) as detailed in Section 7.2.3.3 will be performed.

7.2.4.9 Time to respiratory-related death

Respiratory related causes will be defined as in Section 7.2.3.3. The time to death due to respiratory related causes, in weeks, will be derived as (date of respiratory-related death – date of randomization +1)/7.

If a patient does not die due to respiratory related causes on or prior to Day 379, the same censoring rules will apply as in Section 7.2.3.3.

Cox proportional hazards modelling, as detailed in Section 7.2.3.3, will be performed.

7.2.4.10 Change in FVC expressed in mL over 52 weeks for subjects who have never been treated with pirfenidone or nintedanib

The same data source and analyses (random coefficients regression model) as detailed in Section 7.2.1 will be used. Statistical analysis will be performed for the Primary Population and descriptive analyses only for the SoC2 / Monotherapy Population.

7.2.5 **Exploratory Endpoints**

Unless otherwise stated, exploratory endpoints will be summarized in the Primary Population only, using the mITT analysis set.

7.2.5.1 Biomarkers

Biomarker results will be provided by the central laboratory in standard units. The results, change from baseline and percentage change from baseline (for post baseline assessments) will be summarized by visit.

Correlation analyses assessing the relationship between Biomarker results and efficacy/safety endpoints may be performed.

7.2.5.2 Time to initiation of pirfenidone or nintedanib treatment for SoC2 subjects recruited to the original study design

Only the SoC2 / Monotherapy Population will be used, with only subjects recruited to the original study design (pre-Protocol V6.0).

The time to initiation of pirfenidone or nintedanib treatment will be derived from the 'Pirfenidone/Nintedanib Usage' eCRF. The time to initiation of pirfenidone or nintedanib treatment in weeks will be derived as (date of first initiation of pirfenidone or nintedanib treatment – date of randomization +1)/7.

Time to initiation will be summarized descriptively by treatment.

7.2.5.3 Time to termination of pirfenidone or nintedanib treatment

Summaries of time to termination of pirfenidone or nintedanib treatment will be conducted only for the SoC1 / Combination Population.

The time to termination of pirfenidone or nintedanib treatment will be derived from the 'Pirfenidone/Nintedanib Usage' eCRF. The time to termination of pirfenidone or nintedanib treatment in weeks will be derived as (date of last dose of pirfenidone or nintedanib

treatment – date of randomization +1)/7.

Time to termination of pirfenidone or nintedanib treatment in the SoC1 / Combination Population will be summarized descriptively.

7.2.5.4 Pharmacogenetics

Pharmacogenetic results will be provided by the central laboratory. The results will be summarized by treatment group.

The primary and key secondary endpoint subgroup analyses may be repeated including a post-hoc classification of pharmacogenetic results as a subgroup.

Additional analyses assessing the relationship between Pharmacogenetic results versus safety endpoints may also be performed.

7.3 Safety

Safety evaluations will be performed on the Safety Set, unless otherwise specified. Missing assessments will not be imputed unless stated otherwise. All analyses will be conducted on the Primary Population. Key safety will also be summarized for the SoC1 / Combination and SoC2 / Monotherapy Populations, as detailed in the individual sections.

7.3.1 Exposure and Treatment Compliance

Details of exposure and treatment compliance will be summarized for the mITT Analysis Set, as well as for the Safety Analysis Set. In addition, for the Primary Population only, exposure and compliance will be summarized in the PP Analysis Set.

Date of first dose of study treatment will be derived as the earliest date of drug dispense from the 'Treatment Compliance' eCRF forms.

Extent of exposure to GB0139 (mg) or Placebo will be calculated based on information from the 'Treatment Compliance' eCRF forms. The number of capsules used will be derived as the number of GB0139 capsules dispensed minus the number of unused GB0139 capsules returned during the study. The number of GB0139 capsules used and the dose of GB0139 in the capsules known to have been dispensed will be used to derive the extent of exposure (mg) to GB0139.

The duration of exposure to GB0139 in days will be calculated as the date of last dose recorded in the 'Disposition Study Completion' eCRF minus the date of first dispensing of GB0139 + 1.

The duration of exposure to GB0139 will be summarized both as a continuous variable and categorically, with categories 0-13 weeks, >13 weeks – 26 weeks, >26 weeks=39 weeks, >39 weeks – 52 weeks, > 52 weeks.

The extent of exposure (mg) will be summarized as a continuous variable by treatment group.

The extent (mg) and duration of exposure (days) between each dispensing and returning of study drug will be presented in the listings but will not be summarized.

The duration of exposure to nintedanib or pirfenidone during treatment with study drug will be derived based on the start and stop dates of nintedanib and pirfenidone from the 'Pirfenidone/Nintedanib Usage' eCRF and the first and last date of study drug.

The expected treatment exposure (capsules) will be derived using the treatment duration with study drug multiplied by 2 (the planned daily number of capsules).

Treatment compliance based on dispensing data will be derived as 100 x treatment exposure (capsules) / expected treatment exposure for duration of study treatment through study treatment discontinuation (capsules).

The treatment exposure to study drug (capsules), treatment duration with study drug (days) and treatment compliance (continuous and grouped as < 80%, 80% to 120%, > 120%) will be summarized.

The treatment exposure to study drug (capsules), treatment duration with study drug (days) and treatment compliance between each dispensing and returning of study drug will be presented in the listings but will not be summarized.

Summaries will be repeated in the SoC1 / Combination and SoC2 /Monotherapy Populations. In the SoC1 / Combination Population treatment compliance will be repeated by baseline SoC treatment at baseline (Nintedanib vs Pirfenidone vs Pirfenidone and Nintedanib).

7.3.2 Adverse Events

Adverse events (AEs) from the 'Adverse Events' eCRF will be coded for summarization using the most recent upversioned MedDRA coding as specified in the DMP. In the event that no

coding information is available for a specific AE, the AE will be presented as an "Uncoded" in summary tables.

A Treatment Emergent AE (TEAE) is defined as any protocol defined AE (collected as a unique record from the AE eCRF page) with an onset between the date of first dispensing of study drug (from the 'Treatment Compliance' eCRF forms) and date of last dose recorded + 14 days inclusive (date of last dose from the 'Disposition Study Completion' eCRF). If the date of onset is the same as the date of first dispensing of study drug, then the recorded start of event relative to first dose from the eCRF (before/after) will be used to classify the AE as either a TEAE (after) or a non-TEAE (before).

Missing and/or incomplete dates/times for AEs will not be imputed. For partial/missing dates:

- If the start or stop month/year (if day is missing) or year (if day and month are missing) of the AE is prior to the respective month/year or year of the first dose of study drug, then the AE will be classed as a Non-TEAE.
- If the start month/year (if day is missing) or year (if day and month are missing) of the AE is after the respective month/year or year of the last dose of study drug + 30 days, then the AE will be classed as a Non-TEAE.
- Otherwise, the AE will be classed as a TEAE.

For TEAE summaries presenting the incidence frequency and percentage, the number of actual unique TEAEs (meeting each criteria) will also be presented. For incidence summaries, a subject with multiple TEAEs will contribute only once to the count for a given summary and the maximum severity and relationship will always be used. The number of unique TEAEs will always be presented as per the severity and relationship for the unique TEAEs. Missing relationship will be considered related to study drug and missing severity will be considered severe.

The number and percentage of subjects reporting at least one of the following will be summarized:

- TEAE
- TEAE by maximum severity (overall and within related TEAEs)
- TEAE by maximum relationship to study drug (overall and within serious TEAEs)
- Serious TEAE
- TEAE leading to treatment discontinuation
- TEAE leading to death
- All deaths (Note: time to death is limited to a follow-up period of Day 379)

Further summaries by SOC and PT will be produced for all TEAEs, TEAEs by SoC, PT and maximum severity, treatment related TEAEs, serious TEAEs, TEAEs leading to treatment discontinuation and TEAEs leading to death. These will be presented by SOC and PT, sorted by decreasing frequency overall and then alphabetically. An additional summary all AEs post follow-up (i.e. post treatment end date + 14) will be produced by SOC and PT.

Additional summaries of all TEAEs and of serious TEAEs by PT only, sorted by decreasing frequency overall, will be presented.

Summaries of COVID related (per eCRF) TEAEs and serious COVID related TEAEs will also be produced. In addition, summaries of TEAEs and Serious TEAEs related to IPF exacerbations (i.e. those events marked on the eCRF as related to IPF exacerbation) will be provided.

Serious TEAEs and TEAEs leading to discontinuation of study drug will be presented separately for the SoC1 / Combination and SoC2 / Monotherapy Populations.

Additionally, the incidence of by time period (0 - 13 weeks, >13 weeks – 26 weeks, >26 weeks - 39 weeks, >39 weeks – 52 weeks, ≥ 52 weeks) will be presented. The presentation will include all TEAEs, serious TEAEs, TEAEs leading to treatment discontinuation, and TEAEs leading to death. The denominator for each period will be the number of subjects on treatment at the beginning of that time period. This summary will be repeated for the SoC1 / Combination and SoC2 / Monotherapy Populations.

Each TEAE event rate (per 100 patient years) will also be summarised by preferred term within each system organ class. For each preferred term, the event rate will be presented and will be defined as the number of patients with that AE divided by the sum of the duration from the start of treatment to 14 days after the last treatment dose (for patients without the event) and the time to the AE (for patients with the event) in each group multiplied by 100. This will also be repeated for serious TEAEs.

Risk differences for proportion of subjects with the following TEAEs (with associated 95% confidence intervals) comparing GB0139 groups to Placebo will be estimated:-

- TEAE
- TEAE by maximum severity (overall and within related TEAEs)
- TEAE by maximum relationship to study drug (overall and within serious TEAEs)
- Serious TEAE
- TEAE leading to treatment discontinuation
- TEAE leading to death

Separate subject listings will be provided for AEs leading to death (including a flag for TEAEs), Serious TEAEs and TEAEs leading to treatment discontinuation. A listing of all deaths will also be produced.

7.3.3 Major Adverse Cardiovascular Events (MACE)

Cardiac events of interest will be defined as the following preferred terms:

- Torsade de Pointes
- Ventricular tachycardia
- Ventricular fibrillation
- Ventricular flutter
- Syncope
- Seizures
- Sudden death
- Sudden cardiac death

A summary table of these 8 terms by PT only will be provided, with all terms included in the table even when the number of events is zero.

MACE will be summarized for the Primary, SoC1 / Combination and SoC2 / Monotherapy Populations. A supporting listing will be provided, with a flag for treatment emergent MACE.

7.3.4 Laboratory Data

Système International (SI) units provided by a central laboratory will be used for presenting all laboratory values.

Values below the lower limit of quantification (LLOQ) will be replaced by the value of the LLOQ.

The hematology and clinical chemistry parameters to be summarized are as follows:

- Hematology: Hematocrit, Hemoglobin, Leukocytes with differential count, Platelet (count)
- Clinical chemistry: Albumin, Alkaline phosphatase (ALP), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Bilirubin (total), Calcium, Creatinine, Glucose, Potassium, Sodium

The values provided by the central laboratory in standard units as well as the flags for Low/Normal/High (L/N/H) values relative to the normal range or Normal/Abnormal classifications will be used for summaries.

For the continuous parameters, the results and the change from baseline (for post baseline assessments) will be summarized by treatment and visit. This summary will be repeated in the SoC1 / Combination and SoC2 / Monotherapy Populations.

For any categorical parameters (including incidence of abnormalities), the results will be summarized by treatment and visit based on the number of subjects with non-missing data at the visit as the denominator.

Separate subject listings of abnormalities across all populations, sorted by SoC, will be presented showing all data within the abnormal parameter over the study for the respective subject.

All laboratory results will be listed, including all unscheduled visits.

Serum pregnancy results (at screening) and urinary pregnancy results (post-screening) will be listed per subject and visit.

7.3.5 Vital Signs (including Pulse Oximetry)

Vital signs (including Pulse Oximetry) data from the 'Vital Signs – Complete', 'Vital Signs – Brief' and 'Pulse Oximetry' eCRFs will be used.

The vital sign parameters to be summarized are

- Diastolic and systolic blood pressure (mmHg),
- Heart rate (beats/min),
- Body temperature (°C),
- Respiratory rate (breaths/min),
- Hemoglobin saturation with oxygen (%),
- Body weight (kg),
- BMI (kg/m^2).

If body temperature is recorded in °F then the following formula will be applied:-

Temperature (°C) = 5/9 x (Temperature [°F]-32)

The results and the change from baseline (for post baseline assessments) will be summarized by treatment and visit for each parameter, repeated for all populations.

7.3.6 ECG

ECG data from the 'Electrocardiogram Local' eCRF will be used.

The ECG parameters to be summarized are

- ECG Mean Heart Rate (beats/min),
- PR Interval (msec),
- QRS Duration (msec),
- QT Interval (msec),
- QTcF (Fridericia's Correction Formula) (msec).

The results and the change from baseline (for post baseline assessments) will be summarized by treatment and visit for each parameter.

The overall ECG interpretation (Normal/ Abnormal – Not Clinically Significant [NCS]/ Abnormal – Clinically Significant [CS]) will be summarized by visit based on the number of subjects with non-missing data at the visit as the denominator.

Each of the above summaries will be repeated for the SoC1 / Combination and SoC2 / Monotherapy Populations.

Separate subject listings of CS abnormalities across all populations, sorted by SoC, will be presented showing all data within the CS abnormal parameter over the study for the respective subject.

7.3.7 Physical Examination

Physical Exam data from the 'Physical Exam' eCRF will be used.

The results of the physical examination (Normal, Abnormal – NCS, Abnormal – CS) will be summarized by treatment and visit for each body system. These summaries will be repeated for all populations.

Separate subject listings of CS abnormalities across all populations, sorted by SoC, will be presented showing all data within the CS abnormal body system over the study for the respective subject.

7.3.8 Time to Premature Treatment Discontinuation

The date of premature treatment discontinuation will be derived from the 'Disposition Study Completion' eCRF.

The time to premature treatment discontinuation (i.e. prior to Day 358, Week 52 – 1 week) in weeks will be derived as (date of treatment discontinuation – date of randomization +1)/7.

If a subject does not prematurely discontinue treatment prior to Day 358, they will be censored in the analysis at Day 359.

Summary tables of the time to premature treatment discontinuation by treatment group (as a continuous variable for those that prematurely discontinued), as well as Kaplan Meier plots by treatment will be produced. These summaries and plots will be repeated for all populations.

7.3.9 COVID-19

Cases of Covid-19 will be obtained from the 'Covid-19' eCRF form. Cases post first dose of study treatment will be summarized by treatment arm and split into the following periods:-

- Overall
- On treatment
- Post treatment

These summaries will be repeated for all populations.

8. REFERENCES

1. GALACTIC-1 Clinical Trial Protocol v7.0
2. GALACTIC-1 Case Report Form v156, Nov 2021.
3. ICH E3 Guideline Ref
4. ICH E9 Guideline Ref
5. Fainberg HP, Oldham JM, Molyneau PL, et al. Forced vital capacity trajectories inpatients with idiopathic pulmonary fibrosis: a secondary analysis of a multicentre, prospective, observational cohort. Lancet Digit Health 2022; published online Nov 1. https://doi.org/10.1016/ S2589-7500(22)00173-X

The relevant study documents referenced were the current version at the time of SAP finalization. Should a study document above postdate the SAP sign-off then that version will be used.

9. CHANGES TO STATISTICAL ANALYSIS FROM PROTOCOL

The following clarifications have been made compared to the statistical analysis documented in the protocol at the time of writing (Version 7.0, 28 January 2022):

The protocol stated that two separate sensitivity analyses would be carried out for the primary estimand, and a tipping point analysis. The tipping point analysis described was looking for the tipping point between two sensitivity analyses, rather than relating to the primary analysis, and so was considered not to be informative and was removed. The second sensitivity analysis was also removed.

The protocol stated that for the endpoint of time to death, if fewer than 5% of subjects experienced the event during the study then only frequencies per treatment group would be displayed and no formal statistical analysis would be performed. The threshold for deaths has been removed and time to death will be analyzed regardless of the number of events.

In the logistic regression analyses the Wald test will be used rather than a likelihood ratio test.

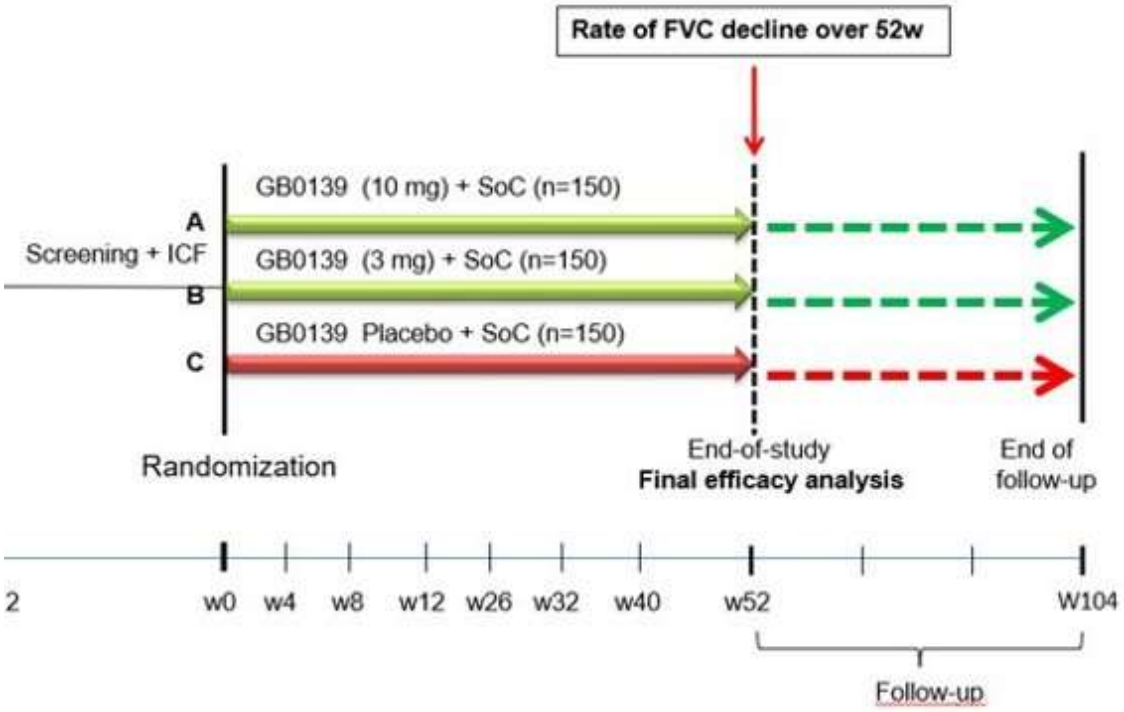
The protocol defined a subgroup of subjects recruited prior to Protocol version 6.0 vs subjects recruited post v6.0, which is also removed.

10. AMENDMENT HISTORY OF SAP

Not Applicable.

11. APPENDICES

11.1 Figure 3: Trial Design Schematic, Original Design



11.2 Table 4: Schedule of Assessments

Visit	1	2	3	4	5	6	7	8	Withdrawal[9]	Follow up[7]
	Screening[1]	Baseline	Treatment							
		0	4	8	12	26	40	52	-	
Day			29	57	85	183	281	365		7 days after final study visit (+7 days)
Time window	6 weeks	0	±3	±3	±3	±7	±7	±7		
Informed consent	X									
HRCT sent to central review	X									
Demographics (including height, weight)	X									
Medical history	X									
Randomization		X								
In- /exclusion criteria	X	X								
Physical examination, vital signs	X	X	X	X	X	X	X	X	X	
HRQoL (SGRQ, SF-36)		X			X	X		X		
Dyspnoea index (UCSD-SOBQ)		X			X	X		X		
12-lead ECG	X	X	X	X	X	X		X	X	
Laboratory test (chemistry, haematology)[2]	X	X	X	X	X	X	X	X	X	
Urinalysis	X			X	X	X	X	X	X	
Pregnancy test[3]	X	X		X		X		X	X	
Biomarker sample		X	X		X	X		X		
Genetics sample[4]		X								
Spirometry (FVC, FEV1)	X	X	X	X	X	X	X	X	X	
SpO_2		X						X		
DLCO	X							X	X	

6MWT		X							XX	
Administer 1st study medication (at clinic) and inhaler training[5]		X								
Dispense trial drug		X	X	X	X	X	X			
Compliance / drug accountability[6]			X	X	X	X	X	X	X	
Adverse events and conc. Meds[8]	X	X	X	X	X	X	X	X	X	X

Notes:

1. HRCT confirmation by central reading must be obtained as soon as possible following screening visit 1 and prior to visit 2

2. See Table 2 and Table 3 in Section 10.4.9 of the protocol.

3. In women of child bearing potential only: serum b-HCG will be required at visit 1 only, followed by urinary testing at subsequent visits.

4. This is optional and separate consent must be obtained. The sample can be taken at other study visits.

5. Subjects should be observed for 1 hour after the first dose to monitor for any acute adverse effects of study drug administration.

6. Includes checking the subject's use of the DPI device (Plastiape monodose inhaler).

7. The follow-up will be performed via a phone call.

8. Events occurring prior to randomization and administration of drug are considered as pre-treatment. Adverse events are also collected for up to the phone follow up.

9. FVC, DLCO and 6MWT will be performed as part of the withdrawal assessments.

11.3 Primary Estimand Sensitivity and Tipping Point Analyses

A sensitivity analysis to test the robustness of the MAR assumption used in the main estimand analysis will be performed to assess the results with missing Week 52 FVC data.

Non-monotone missing data or missing data at other visits before week 52 will not be imputed. Multiple imputation will be used to handle missing data at week 52. The imputation model will be similar to the statistical model of the primary analysis.

For the imputation of week 52 data that is not available for reasons other than the occurrence of an ICE, the imputation model will be run on the subset of patients who prematurely discontinued trial drug but have been followed up for FVC measurements at week 52. FVC measurements that remain unobserved due to ICEs will still be handled as described in Section 7.2.1. Table 5 below contrasts the MAR approach used in the main estimand analysis with the MNAR approach used in the sensitivity analysis.

Table 5 – Missing Data Approaches

Analysis	**No FVC result but alive at Week 52**	
	Handling of missing FVC result	**Underlying assumption**
Primary Estimand Analysis	Missing data handled by model.	Assumes missing at random. Discontinued subjects would have behaved similarly to subjects who did not discontinue who are in the same treatment group.
Sensitivity analysis	Based on the slope estimates for GB0139 dose and placebo among subjects who experience ICE without missing FVC data.	Subjects with a missing result would have behaved similarly to discontinued subjects with a result who are in the same treatment group.

The slope (SE) estimates of both treatment groups will be used in the sensitivity analysis. This approach is considered appropriate since the reasons for trial drug termination are expected to be similar between subjects with and without missing FVC data (discontinuation mainly due to AEs). The Sensitivity analysis corresponds to the assumption that in subjects with missing FVC data, the treatment effect would have persisted in the same manner as for subjects without missing FVC after trial drug discontinuation.

The number of imputations will be set to 1000 in order to ensure adequate efficiency for the estimation of missing data. For each imputed dataset, the same statistical model as defined for

the primary analysis will be used for the analysis. See Section 7.2.1 for a description of the primary analysis model. The results will be pooled following the standard multiple imputation procedure. See Section 11.4 for further information on the implementation of the multiple imputation approach.

If the primary analysis and sensitivity analysis reach differing conclusions a tipping point analysis will be done. The tipping point analysis will be performed by applying an incremental shift from the imputed FVC value generated under MAR assumption toward the imputed FVC value generated under the MNAR assumption. The value of the shift that overturns the primary analysis result will represent the tipping point.

11.4 Multiple Imputation Procedure

The following steps provide guidance on how missing FVC data at week 52 will be implemented using multiple imputation to allow sensitivity analyses of the primary endpoint. Refer to Section 11.3 for the description of the sensitivity analyses regarding handling of missing data.

Step 1: Run Primary Analysis Model on Observed Data

Run the primary analysis model to get the slope estimates with standard errors (SE) for each treatment group. Let $\hat{\beta}_T$ and $\hat{\sigma}_T$ denote the slope and SE estimates in treatment group GB0139 3mg and $\hat{\beta}_P$ and $\hat{\sigma}_P$ the slope and SE estimates for placebo.

Step 2: Draw 1000 mean imputation slopes for each treatment

Let β_T and β_P represent the true slopes in drug and placebo respectively with $f(\beta_T) \sim N(\hat{\beta}_T, \hat{\sigma}_T^2)$ and with $f(\beta_P) \sim N(\hat{\beta}_P, \hat{\sigma}_P^2)$, using the slope (SE) estimates obtained in step 1. Draw 1000 random slopes from the appropriate distribution (see Section 11.3) for each treatment.

Step 3: Draw 1000 slopes for each subject

From the respective SE for each treatment slope from step 1, derive an approximation for the SD as SE*sqrt(n) where n is the number of subjects in the model randomized to the relevant treatment. For each mean imputation slope obtained in step 2, draw an individual slope for each subject randomized to the respective treatment from a normal distribution with mean equal to the mean imputation slope and relevant SD as derived above.

Step 4: Impute any monotonic missing FVC data at 52 weeks using each slope

a) Considering that the withdrawal of a subject leading to missing data can occur at any time during the study, the timepoint of the last available FVC value has to be taken into account to impute the missing FVC value at 52 weeks:
b) $\text{FVC week 52 imputed}_{ij} = \text{last FVC value available}_i + \hat{\beta}_{ij} *$ (time between date of last FVC value available i and planned 52 week timepoint [days])

where i denotes the indicator of the ith subject, j the indicator of the jth imputation and $\hat{\beta}_{ij}$ denotes a random slope sampled from the distribution mentioned above for the i-th subject in the j-th imputation.

c) Create 1000 imputed FVC datasets for subjects with monotonic missing FVC data at 52 weeks including replicates of any FVC data collected in the study with the addition of the imputation specific 52 week result.
d) Create 1000 identical FVC datasets for subjects with no monotonic missing FVC data at 52 weeks.
e) Combine data from b and c.

Step 5: Run primary analysis model on each imputed dataset

Run the model of the primary analysis on each imputed dataset, using a "by _IMPUTATION_ " statement to obtain 1000 parameter estimates (variable = estimate) and standard errors (variable = stderr).

Step 6: Combine the results obtained in step 4 using PROC MIANALYZE

```
Ods output ParameterEstimates=step5;
Proc Mianalyze data=step5 ;
modeleffects estimate;
stderr stderr;
Run;
```

11.5 SAS Code

11.5.1 Primary analysis

```
ods output estimates=tests tests3=fixed;
proc mixed data=adeff;
     where paramcd='FVC';
      class subjid trt01pn;
      model cfb  = base areltm  trt01pn trt01pn*areltm /ddfm=kr s residual outp=resplot;
      random intercept areltm /  sub = subjid type = un;
      estimate 'Plc Slope' areltm 1 trt01pn*areltm 1 0/cl;
      estimate '3mg Slope' areltm 1 trt01pn*areltm 0 1/cl;
      estimate 'Slope 3mg v Plc' trt01pn*areltm 1 -1/cl;
run;
```

where
subjid = Subject ID
trt01pn = Randomized treatment group (1=Placebo, 2= GB0139 3mg)
base=Baseline FVC for the subject
areltm = Years since first dose
cfb = Change from baseline in FVC
<mean baseline FVC> = the mean of the variable base across all records in the dataset FVC relating to the population of interest (i.e. all records to be included in the model)

11.6 SGRQ Scoring

11.6.1 Item Weights

The following weights are applied if the subject gives a positive response as follows:

PART 1 (one response per question)

1) Over the last year, I have coughed:
Most 80.6
Several 63.2
A few 29.3
Only 28.1
Not 0.0

2) Over the last year, I have brought up phlegm (sputum):
Most 76.8
Several 60.0
A few 34.0
Only 30.2
Not 0.0

3) Over the last year, I have had shortness of breath:
Most 87.2
Several 71.4
A few 43.7
Only 35.7
Not 0.0

4) Over the last year, I have had attacks of wheezing:
Most 86.2
Several 71.0
A few 45.6
Only 36.4
Not 0.0

5) During the last year, how many severe or very bad unpleasant attacks of chest trouble have you had?
More than three 86.7
3 attacks 73.5
2 attacks 60.3
1 attack 44.2
None 0.0

6) How long did the worst attack of chest trouble last?
a week or more 89.7
3 or more days 73.5

1 or 2 days 58.8
less than a day 41.9

7) Over the last year, in an average week, how many good days (with little chest trouble) have you had?
None 93.3
1 or 2 76.6
3 or 4 61.5
nearly every day 15.4
every day 0.0

8) If you have a wheeze, is it worse in the morning?
No 0.0
Yes 62.0

PART 2

9) How would you describe your chest condition? (one response)
The most important problem I have 83 .2
Causes me quite a lot of problems 82.5
Causes me a few problems 34.6
Causes no problem 0.0

10) If you have ever had paid employment? (one response)

My chest trouble made me stop work 88.9
My chest trouble interferes with my work or made me change my work 77.6
My chest trouble does not affect my work 0.0

11) Questions about what activities usually make you feel breathless (all that apply).
Sitting or lying still 90.6
Getting washed or dressed 82.8
Walking around the home 80.2
Walking outside on the level 81.4
Walking up a flight of stairs 76.1
Walking up hills 75.1
Playing sports or games 72.1

12) More questions about your cough and breathlessness (all that apply).
My cough hurts 81.1
My cough makes me tired 79.1
I get breathless when I talk 84.5
I get breathless when I bend over 76.8
My cough or breathing disturbs my sleep 87.9
I get exhausted easily 84.0

13) Questions about other effects your chest trouble may have on you (all that apply).
My cough or breathing is embarrassing in public 74.1
My chest trouble is a nuisance to my family, friends or neighbours 79.1
I get afraid or panic when I cannot get my breath 87.7
I feel that I am not in control of my chest problem 90.1
I do not expect my chest to get any better 82.3
I have become frail or an invalid because of my chest 89.9
Exercise is not safe for me 75.7
Everything seems too much of an effort 84.5

14) Questions about your medication (all that apply).
My medication does not help me very much 88.2
I get embarrassed using my medication in public 53.9
I have unpleasant side effects from my medication 81.1
My medication interferes with my life a lot 70.3

15) Questions about how activities may be affected by your breathing (all that apply).
I take a long time to get washed or dressed 74.2
I cannot take a bath or shower, or I take a long time 81.0
I walk more slowly than other people, or I stop for rests 71.7
Jobs such as housework take a long time, or I have to stop for rests 70.6
If I walk up one flight of stairs, I have to go slowly or stop 71.6
If I hurry or walk fast, I have to stop or slow down 72.3
My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, play bowls or play golf 74.5
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim 71.4
My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports 63.5

16) We would like to know how your chest trouble usually affects your daily life (all that apply).
I cannot play sports or games 64.8
I cannot go out for entertainment or recreation 79.8
I cannot go out of the house to do the shopping 81.0
I cannot do housework 79.1
I cannot move far from my bed or chair 94.0

17) Tick the statement which you think best describes how your chest affects you (tick one).
It does not stop me doing anything I would like to do 0.0
It stops me doing one or two things I would like to do 42.0
It stops me doing most of the things I would like to do 84.2
It stops me doing everything I would like to do 96.7

11.6.2 **Scoring**

The weights from each question included in each component will be summed as follows:

Symptoms Component: questions 1-8 (max score 662.5).

Activity Component: questions 11 and 15 (max score 1209.1).

Impacts Component: questions 9-10, 12-14 and 16-17 (max score 2117.8).

Total Score: questions 1-17 (max score 3989.4).

Each component score will be calculated as: 100 x Summed weights for each question in that component / max score

If multiple responses are given in error then the average weight will be used for the question.

If there are missing items (depending on expected response), the maximum weight for the missing item will be subtracted from the max score in the denominator. The maximum number allowable missing items in each component are as follows: Symptoms Component – 2 items, Activity Component – 4 items, Impacts Component – 6 items.

11.7 UCSD - SOBQ

When I do, or if I were to do, the following tasks, I would rate my breathlessness as:

0 None at all
1
2
3
4 Severe
5 Maximal or unable to do because of breathlessness

1. At rest
2. Walking on a level at your own pace
3. Walking on a level with others your age
4. Walking up a hill
5. Walking up stairs
6. While eating
7. Standing up from a chair
8. Brushing teeth
9. Shaving and/or brushing hair
10. Showering/bathing
11. Dressing
12. Picking up and straightening
13. Doing dishes
14. Sweeping /vacuuming
15. Making bed
16. Shopping
17. Doing laundry
18. Washing
19. Mowing lawn
20. Watering lawn
21. Sexual activities
22. Shortness of breath
23. Fear of "hurting myself" by overexerting
24. Fear of shortness of breath

11.8 SF-36 Scoring

The SF-36 (version 2) consists of 36 items. The 36 questions are:

1: In general, would you say your health is

2: Compared to one year ago, how would you rate your health in general now

3A: Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports

3B: Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

3C: Lifting or carrying groceries

3D: Climbing several flights of stairs

3E: Climbing one flight of stairs

3F: Bending, kneeling, or stooping

3G: Walking more than a mile

3H: Walking several hundred yards

3I: Walking one hundred yards

3J: Bathing or dressing yourself

4A: As a result of your physical health, cut down on the amount of time you spent on work or other activities

4B: As a result of your physical health, accomplished less than you would like

4C: As a result of your physical health, were limited in the kind of work or other activities

4D: As a result of your physical health, had difficulty performing the work or other activities (for example, it took extra effort)

5A: As a result of any emotional problems, cut down the amount of time you spent on work or other activities

5B: As a result of any emotional problems, accomplished less than you would like

5C: As a result of any emotional problems, did work or other activities less carefully than usual

6: During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups

7: How much bodily pain have you had during the past 4 weeks

8: During the past 4 weeks how much did pain interfere with your normal work (including both work outside the home and housework)

9A: How much of the time during the past 4 weeks: did you feel full of life

9B: How much of the time during the past 4 weeks: have you been very nervous

9C: How much of the time during the past 4 weeks: have you felt so down in the dumps that nothing could cheer you up

9D: How much of the time during the past 4 weeks: have you felt calm and peaceful

9E: How much of the time during the past 4 weeks: did you have a lot of energy

9F: How much of the time during the past 4 weeks: have you felt downhearted and depressed

9G: How much of the time during the past 4 weeks: did you feel worn out

9H: How much of the time during the past 4 weeks: have you been happy

9I: How much of the time during the past 4 weeks: did you feel tired

10: During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting your friends, relatives, etc.)

11A: I seem to get sick a little easier than other people

11B: I am as healthy as anybody I know

11C: I expect my health to get worse

11D: My health is excellent