# Galecto Biotech AB

## STUDY PROTOCOL

**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**

**Sponsor:** Galecto Biotech AB, Ole Maaloes Vej 3, DK-2200 Copenhagen, Denmark

**Study Number:** GALACTIC-1

**IND Number:** 124075 **EudraCT Number:** 2018-002664-73

**Compound:** GB0139

**Authors:** [redacted]

**Version:** 7.1_UK

**Date:** 28 January 2022

# 1.0 ADMINISTRATIVE

## 1.1 Contacts

A separate contact information list will be provided to each site.

| Contact Type/Role | Europe Contact | USA Contact |
|---|---|---|
| **Serious adverse event and pregnancy reporting** | *See Section 11.0* | *See Section 11.0* |
| **Medical Monitor** | [redacted] | [redacted] |
| **Responsible Medical Officer** | [redacted]<br>PhD<br>Chief Medical Officer<br>Galecto Biotech AB,<br>Ole Maaloes Vej 3,<br>DK-2200 Copenhagen<br>Denmark | [redacted]<br>Chief Medical Officer<br>Galecto Biotech AB,<br>Ole Maaloes Vej 3,<br>DK-2200 Copenhagen<br>Denmark |

## 1.2 Approval

**REPRESENTATIVES of Galecto Biotech AB**

This study will be conducted with the highest respect for the individual subjects in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonization E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

**SIGNATURES**

[redacted] 28 January 2022

Date

Chief Medical Officer, Galecto Biotech AB

[redacted] 28/01/2022

Date

Head of Statistics, Galecto Biotech AB

## INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, package insert, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 11.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Responsibilities of the Investigator (A).

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

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## 2.1 Study Synopsis

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<tr><td>Title of Protocol:<br>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</td><td>IND No.: 124075</td><td>EudraCT No.:<br>2018-002664-73</td></tr>
<tr><td>Study Number: GALACTIC-1</td><td colspan="2">Phase: IIb</td></tr>
<tr><td>Co-ordinating Investigator</td><td colspan="2">[redacted]<br>Keck School of Medicine of USC<br>University of Southern California<br>Department of Medicine<br>Division of Pulmonary, Critical Care and Sleep Medicine<br>2020 Zonal Avenue, IRD 724<br>Los Angeles, CA 90033</td></tr>
<tr><td colspan="3">Overview (Figure 1)<br>Population:<br>All subjects enrolled into the study will have a diagnosis of IPF established within the previous five years, and a diagnostic HRCT scan assessed according the ATS/ERS/Fleischner criteria available within the previous 12 months (up to 12 months +27 days).<br><br>Treatment:<br>All subjects eligible for the study will be randomised in a 2:1 ratio to one of two treatment arms:<br>A. GB0139 3mg once a day (2x 1.5mg capsules) by inhalation<br>B. Placebo once a day (2x placebo capsules) by inhalation<br><br>The stratification at randomization and the following SoCs are removed in Protocol version 6.1_UK such that all future participants will not be treated with nintedanib or pirfenidone at screening and ranodmisation:<br>The two strata of Standard of Care (SoC) were as follows in the previous study design:<br>1. SoC1: Subjects currently on treatment with either pirfenidone or nintedanib.<br>2. SoC2: Subjects not currently treated with pirfenidone or nintedanib.</td></tr>
</table>

***Evaluation and follow up:***

From baseline to week 52, visits will be scheduled at weeks 0, 4, 8, 12, 26, 40 and 52 for evaluations according to the Time & Events Table (Section 2.2). A subject's follow-up safety assessment will be performed via a phone call one week after the last study visit.

**Number of Subjects**

Estimated to randomize approximately 141 participants in total

**Dose Level(s)**

- GB0139 3mg once a day (2x 1.5mg capsules) by inhalation
- Placebo once a day (2x placebo capsules) by inhalation

**Duration of Treatment & Follow up**

- 52-weeks treatment after randomisation
- Follow up via a phone call one week after the last study visit

**Main Criteria for Inclusion**

1. Male and female subjects aged ≥ 40 years of age with a diagnosis of IPF established during the previous five years according to ATS/ERS/Fleischner criteria. A historical diagnostic HRCT scan assessed according to the ATS/ERS/Fleischner criteria must be available from within the 12 months (up to 12 months +27 days) prior to screening. Diagnostic HRCTs will be subject to central reading for confirmation.
2. Lung function parameters as follows:
    a. FVC > 45% of the predicted value at screening
    b. DLCO (corrected for Hb) of 30% to 79% of the predicted value at screening.
3. Patients who currently are not being treated with nintedanib or pirfenidone; or cannot tolerate nintedanib or pirfenidone.
4. Subjects must sign and date a written, IRB/EC approved informed consent form and any required authorization prior to initiation of any study procedures.

**Main Criteria for Exclusion**

Subjects meeting any of the following exclusion criteria are not to be enrolled in the study/randomized to treatment:

1. Currently has significant airways obstruction: FEV1/FVC ratio of < 0.7 at screening.
2. Has clinical evidence of active infection, including, but not limited to, bronchitis, pneumonia, sinusitis, urinary tract infection, and cellulitis.
3. Has a history of malignancy within the last 2 years with the exception of basal cell carcinoma, squamous cell carcinoma of the skin (localised, treated or cured), chronic lymphocytic leukaemia (under observation) and prostate cancer requiring anti-androgens, localised treatment (minor surgery, radiotherapy) and/or managed by observation.
4. Has any condition other than IPF that, in the opinion of the investigator, is likely to result in the death of the subject within the next 2 years.

5. Presence of other disease that may interfere with testing procedures or in the judgement of the Investigator may interfere with trial participation or may put the patient at risk when participating in this trial.
6. Is likely to receive lung transplantation within the next 12 months.
7. Currently receiving nintedanib, pirfenidone, high dose corticosteroid, cytotoxic (e.g., chlorambucil, azathioprine, cyclophosphamide, methotrexate), vasodilator therapy for pulmonary hypertension (e.g., bosentan). Also see prohibited medications (Section 8.3.2). A current dose of less than or equal to 15 mg/day of prednisone or its equivalent is acceptable if the dose is anticipated to remain stable during the study.
8. Prior use of GB0139 or previously randomised in GALACTIC-1.
9. Prior use of nintedanib or pirfenidone within 7 days of initiation of screening.
10. Prior use of investigational drugs within 30 days (or 5 half-lives, whichever is longer) of initiation of screening.
11. Participating in another interventional clinical trial.
12. Has a history of unstable or deteriorating cardiac or pulmonary disease (other than IPF) within the previous six months, including, but not limited to, the following:
    a. Unstable angina pectoris or myocardial infarction, or percutaneous coronary intervention within the last 6 months
    b. Congestive heart failure requiring hospitalization
    c. Uncontrolled clinically significant arrhythmias.
13. If female, the subject is pregnant or lactating or intending to become pregnant before participating in this study during the study and within 33 days after last dose of the study drug; or intending to donate ova during such time period.
14. Woman considered to be of childbearing potential who do not use highly effective birth control methods during the study and for 33 days after last administration of study drug.
15. Male partners of women of child bearing potential not committing to using condoms during the course of the study and 90 days after last administration of study drug, unless they have undergone male sterilization.
16. Hypersensitivity to the active substance (GB0139) or the excipient (lactose).

**Study Objectives**

**Primary Objectives**

- 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.

**Secondary Objectives**

- Further characterize the effect of GB0139 compared with placebo over 52 weeks treatment period on FVC, also on the quality of life, time to respiratory-related hospitalizations and all-cause mortality.

**Main Criteria for Evaluation and Analyses**

**Primary Endpoint**

- The annual rate of decline in Forced Vital Capacity (FVC; expressed in mL over 52 weeks)

**Key Secondary Endpoints**

- Proportion of subjects with an absolute decline from baseline in FVC % pred of ≤10% at w52.
- Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at w52.
- Time to first hospitalization (respiratory related, including acute exacerbation of IPF).
- Time to death (all-causes).

Additional secondary and exploratory efficacy variables with bearing on the efficacy of GB0139 (e.g., other QoL) are described in detail in the Main Criteria and Evaluation and Analyses below).

**Other Secondary Endpoints**

- Proportion of subjects with an absolute decline from baseline in FVC % pred of ≤5% at w52
- Change from baseline in 6-minute walk test (6MWT) distance over 52 weeks
- Change in diffusion capacity of the lung for carbon monoxide (DLCO), corrected for Hb
- Change from baseline at week 52 for dyspnoea 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
- Time to initatiation of nintedanib or pirfenidone
- Change in FVC expressed in mL over 52 weeks for subjects who have never been treated with pirfenidone or nintedanib

**Exploratory Endpoints**

- **Biomarkers**: Change from baseline of selected biomarkers. These may include but are not limited to: YKL-40, PAI-1, PDGF-BB, MCP-1, CCL-18, Gal-3, markers of collagen metabolism.
- Time to initiation of pirfenidone or nintedanib treatment for SoC2 participants up to the time when SoC1 and SoC2 were removed in the study
- **Pharmacogenetics**: The study includes a pharmacogenetic component. This is not mandatory in order for a subject to participate in the study.

**Statistical Considerations:**

The primary efficacy analysis will be based on the comparison between the GB0139 3mg group against the Placebo group in patients who were not treated with nintedanib or pirfenidone at screening.

The primary endpoint of this trial, annual rate of decline in FVC, will be analyzed by a random coefficient regression model including treatment group and baseline FVC (mL).

The key secondary endpoints will be analysed as follows: Proportion of participants with an absolute decline from baseline in FVC % predicted of ≤10% at week 52 will be analysed by logistic regression including treatment and baseline FVC (mL) in the model.

Change from baseline in the SGRQ total score at week 52 will be analysed by a mixed model repeated measure.

The time to first hospitalization (any respiratory related) will be analysed by a Cox PH model.

Time to death (all-causes) will be analysed by Cox PH model.

Secondary and further endpoints will be analysed in an exploratory manner.

**Sample size justification:**
The annual decline in FVC for placebo is estimated to be 200ml. 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, with a randomization ratio of 2:1, the study would have 75% power.

## 2.2 Study Time and Events Schedule

### Table 1: Study Time & Events Schedule

| Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | Withdrawal[9] | Follow up[7] |
|---|---|---|---|---|---|---|---|---|---|---|
| | Screening[1] | Baseline | Treatment | | | | | | | |
| Weeks of treatment | | 0 | 4 | 8 | 12 | 26 | 40 | 52 | - | |
| Day<br>Time window | 6 weeks | 0 | 29<br>±3 | 57<br>±3 | 85<br>±3 | 183<br>±7 | 281<br>±7 | 365<br>±7 | | 7 days after final study visit (+7 days) |
| 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, haemtaology)[2] | X | X | X | X | X | X | X | X | X | |
| Urinalysis | X | | X | X | X | X | X | X | X | |
| Pregnancy test[3, 4] | X | X | X | X | X | X | X | X | X | |
| Biomarker sample | | X | X | | X | X | | X | | |
| Genetics sample [5] | | X | | | | | | | | |
| Spirometry (FVC, FEV1) | X | X | X | X | X | X | X | X | X | |
| $SpO_2$ | | X | | | | | | X | | |
| DLCO | X | | | | | | | X | X | |
| 6MWT | | X | | | | | | X | X | |
| Administer 1st study medication (at clinic) & inhaler training[6] | | X | | | | | | | | |
| Dispense trial drug | | X | X | X | X | X | X | | | |
| Compliance / drug accountability[7] | | | X | X | X | X | X | X | X | |
| Adverse events & 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 Section 10.4.9

3. In women of childbearing 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 (e.g., bronchospasm – see Section 8.1)
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 (as defined in Section 11.1.1). 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.

# 3.0 STUDY REFERENCE INFORMATION

## 3.1 Study-Related Responsibilities

Syneos Health and Biorasi the CROs designated to execute the study, will perform all study-related activities as described in this study protocol. IQVIA serves as the central vendor to manage SAE reporting and the study safety database.

## 3.2 Principal Investigator/Principal Coordinator

Galecto Biotech AB together with Syneos Health has selected a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

## 3.3 List of Abbreviations

| | |
|---|---|
| 6MWT | 6 minute walk test |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AM | alveolar macrophages |
| AST | aspartate aminotransferase |
| ATA | American Thoracic Association |
| BAL | bronchoalveolar lavage |
| BALF | bronchoalveolar lavage fluid |
| CHF | congestive heart failure |
| CHI3L1 | chitinase-3-like protein 1 |
| COPD | chronic obstructive pulmonary disease |
| eCRF | electronic case report form |
| CRO | contract research organization |
| HRCT | high resolution computed tomography |
| DLCO | diffusion lung capacity for carbon monoxide |
| ECG | electrocardiogram |
| ECM | extracellular matrix |
| EMA | European Medicines Agency |
| FEV1 | forced expiratory volume in 1 s |
| FDA | Food and Drug Administration |
| FUV | Follow-up Visit |
| FVC | forced vital capacity |
| Gal-3 | galectin-3 |
| GCP | good clinical practice |
| GGT | γ-glutamyl transferase |
| ICH | International Conference on Harmonisation |
| IEC | independent ethics committee |
| ILD | interstitial lung disease |
| IPF | idiopathic pulmonary fibrosis |
| IRB | institutional review board |
| IVRS | interactive voice response system |
| IWRS | interactive web response system |
| NAC | N-acetylcysteine |
| KL-6 | Krebs’ von de Lungen-6 |
| LSLV | last subject last visit |
| MAD | multiple ascending dose |

| | |
|---|---|
| MoA | mechanism of action |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NOAELs | no-observed-adverse-effect-levels |
| NSIP | non-specific interstitial pneumonia |
| MRI | magnetic resonance imaging |
| NYHA | New York Heart Association |
| OD | once per day |
| PAI-1 | plasminogen activator inhibitor 1 |
| PD | progressive disease |
| PDGF | platelet derived growth factor |
| PFT | pulmonary function test |
| PFS | progression-free survival |
| PH | pulmonary hypertension |
| p.o. | per os (oral) |
| PK | pharmacokinetic |
| QoL | quality of life |
| RT | retention time |
| RRT | relative retention time |
| SAE | serious adverse event |
| SAD | single ascending dose |
| SmPC | summary of product characteristics |
| SoC | standard of care |
| TGFβ | transforming growth factor β |
| TLC | total lung capacity |
| TID | three times per day |
| UIP | usual interstitial pneumonia |
| WHO | World Health Organization |
| WBC | Leukocytes (white blood cells) |
| YKL-40 | chinitnase-3-like protein 1 |

# 4.0 INTRODUCTION

## 4.1 Study Background

Idiopathic pulmonary fibrosis (IPF), the most common form of the idiopathic interstitial pneumonias, is a chronic, progressive, irreversible, and usually lethal lung disease of unknown cause. IPF occurs mostly in elderly adults, is limited to the lungs, and is associated with a histopathological or radiological pattern typical of usual interstitial pneumonia (UIP) [1-3]. The disease course is heterogeneous with clinical course highly variable from one subject to another. In general, the clinical course can be relatively slow but progressive or very rapid with deterioration leading to decline in lung function and death. The clinical picture is invariably characterized by worsening cough and dyspnea, respiratory insufficiency and an overall poor prognosis with median survival between 2 to 3 years from diagnosis [4-7].

The cause of IPF is unknown, but it appears to be a disorder likely arising from the interplay between environmental and genetic factors. Cigarette smoking is the most consistent environmental risk factor. Genetic factors have also been strongly implicated in both sporadic IPF and familial pulmonary fibrosis. A growing body of evidence suggests that the disease process is initiated through alveolar epithelial cell microinjuries and apoptosis. Subsequently, fibroblasts proliferate and differentiate into myofibroblasts, leading to the excessive accumulation of extracellular matrix (ECM) components including collagen and fibronectin under the control of profibrogenic stimuli such as transforming growth factor β (TGF-β). The resulting fibrotic tissue is characterized by excessive scarring, organ injury, function decline and organ failure [8-13]. TGF-β has been assigned a clear pathogenic role by its induction of ECM production and apoptosis of alveolar epithelial cells (AECs) in IPF. Inhibiting TGF-β activity, in experimental models of lung fibrosis reduces the fibrosis. [14-23].

The natural history of IPF is heterogeneous; therefore, raising a number of challenges for individual patient management. There are a number of asymptomatic subjects with subclinical, undiagnosed disease, especially among the elderly [24, 25]. Some subjects remain relatively stable for a prolonged period of time, while others progress rapidly [26] and some experience

acute exacerbations of IPF, e.g., acute respiratory worsening [27] of unidentified cause [28] leading to non-elective hospitalization and frequently death [29]. IPF has a broad and profound impact on subjects' health-related quality of life (HRQoL) [30, 31].

Two drug therapies, pirfenidone and nintedanib, are currently licensed for the treatment of IPF. Both therapies are only conditionally recommended by the current official ATS/ERS/JRS/ALAT clinical practice guidelines for the treatment of IPF due to the potentially significant adverse effects with both therapies [36]. Both drugs appear to have comparable efficacy, approximately halving the rate of disease progression over 52 weeks as assessed by decline in FVC when compared with placebo. However, neither has shown clear evidence of a survival or symptomatic benefit [32-35]. Moreover, tolerability limits the use of both drugs in some subjects, and it increasingly recognized that a number of subjects either require a reduced dose or have to stop treatment [36-39]. Hence there remains a significant unmet medical need in IPF.

Although they have been widely used in the past, current evidence does not support the use of corticosteroid or immunosuppressant as a therapy for IPF [3, 40, 41]. Indeed, long-term corticosteroid therapy is associated with significant treatment-related morbidity and various potentially severe side effects. As a result, current evidence-based guidelines [3] provide a strong recommendation against the use of corticosteroid monotherapy in IPF, albeit in the absence of any randomized placebo-controlled trial.

## 4.2 Study Rationale

### 4.2.1 Role of Galectin-3 in fibrosis

Gal-3 is a beta-galactoside-binding mammalian lectin (a carbohydrate binding protein) of approximately 30 kDa which is evolutionarily highly conserved [42]. In multiple models of organ fibrosis, it has been demonstrated that Gal-3 is potently pro-fibrotic, modulating the activity of fibroblasts and macrophages in chronically injured tissues [18, 43-48]. It is hypothesized that increased Gal-3 expression during chronic injury leads to fibroblast activation via the aggregation of growth factor receptor clusters (such as TGF-ß), thereby amplifying pro-

fibrotic signal cascades. Mice that are deficient in Gal-3, although phenotypically normal, develop reduced fibrosis in response to tissue injury in lung, liver, blood vessels, heart, and kidney, and also in response to allograft rejection [43-48]. In addition, preclinical studies using direct intratracheal administration of the galectin-3 inhibitor GB0139 showed that GB0139 decreased bleomycin-induced fibrosis when administered during the fibrotic phase in mice [18, 49]. Thus, Gal-3 may be an important regulator of fibrosis, and these pre-clinical studies provide a proof of principal that inhibition of Gal-3 in man could be a potential novel therapeutic strategy. Gal-3 is up-regulated in subjects with IPF with elevated levels of Gal-3 in bronchoalveolar lavage fluid and serum [18] but not in non-specific interstitial pneumonia (NSIP), suggesting that Gal-3 may be a more specifically associated with disease pathogenesis and outcome in IPF. Gal-3 is also upregulated during acute exacerbations of IPF. Gal-3 expression is also up-regulated in other chronic fibroses, including fibrotic liver disease, regardless of etiology [44]. Together, these observations support the development of Gal-3 selective inhibitors for IPF.

GB0139 is a small molecule lectin inhibitor designed specifically to modulate the fibrogenic response to tissue injury. GB0139 has been formulated for inhaled delivery to both target the disease site in the periphery of the lung in IPF more directly, and to limit any potential systemic toxicity. More details on the profile of GB0139 be found in the Investigator's Brochure (IB).

Galecto Biotech AB conducted a phase 1 clinical study in human volunteers and in 24 subjects with IPF in which GB0139 was delivered once daily by dry powder inhalation using a Plastiape device. The trial was divided into two parts. Part 1 (single ascending dose) explored the safety and tolerability of GB0139 in healthy volunteers. Part 2 (IND opening study) investigated the safety, tolerability pharmacokinetics and pharmacodynamics in subjects with IPF. The clinical protocol was discussed with the FDA during a pre-IND meeting held on 03 December 2014, and the changes suggested by the Agency were implemented before Part 2 of the protocol was conducted under the IND.

The results from clinical trial GB-HV-01 confirm that GB0139 is safe and well tolerated at single inhaled doses up to 50 mg in healthy volunteers [Single Ascending Dose (Part 1)], and multiple inhaled doses up to 10 mg daily in IPF subjects during 2 weeks of treatment [Multiple Ascending Dose (Part 2)]. Further, GB-HV-01 demonstrated that GB0139 reaches the alveolar macrophages at pharmacologically relevant concentrations and causes a dose-dependent reduction in cell surface Galectin-3 in participants with IPF. In addition, dose-response related reductions were observed in the plasma levels of putative IPF biomarkers (YKL-40, PAI-1, PDGF-BB, and CCL18), which have been associated with IPF disease severity and all-cause mortality [50].

Based on both preclinical and available clinical data, GB0139 is expected to demonstrate a favourable risk/benefit profile compared with existing treatment options. No dose-limiting toxicity has been observed in preclinical testing. In addition, the inhaled route of delivery targets the site of the disease directly, with the potential to limit systemic side effects.

## 5.0 STUDY OBJECTIVES

### 5.1 Primary Objective

The primary objective of the study is 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.

### 5.2 Secondary Objective

The secondary objective of the study is to further characterize the effect of GB0139 compared with placebo over 52 weeks treatment period on FVC, also on the quality of life, time to respiratory-related hospitalizations and all-cause mortality.

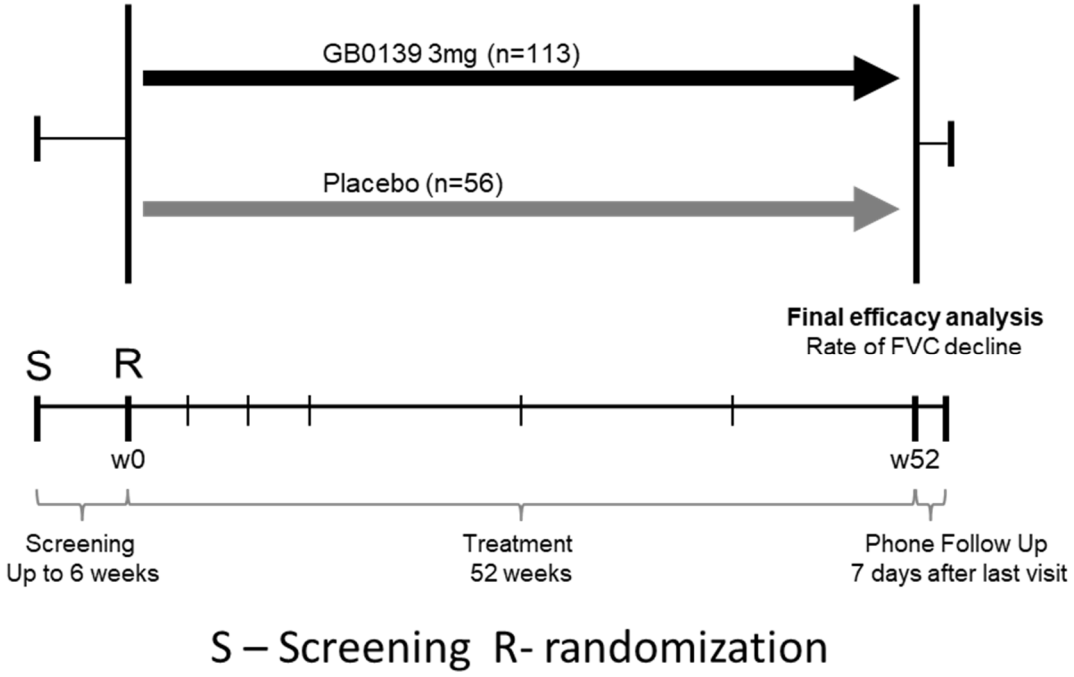
# 6.0 STUDY DESIGN

## 6.1 Overall design

Following a review of unblinded efficacy and safety data by the study's DSMB in Feb2021, the study design is modified based on the DSMB's recommendation. DSMB has recommended the participants randomised to the 10 mg GB0139 group and all those currently taking nintedanib or pirfenidone should be discontinued from the study. Galecto expects to continue recruiting participants who are not taking nintedanib or pirfenidone at screening and who would be randomised to receive 3 mg GB0139 or placebo.

This remains a multicenter, randomized, double-blind, placebo-controlled trial in subjects with IPF. The updated design based on the above DSMB's recommendation is summarized in Figure 1 below.

**Figure 1: Study Schematic Diagram**



There are three study periods:

Screening Period – After signing the study inform consent form (ICF) participant will enter a screening period up to 6 weeks.

Treatment Period- Following randomization, eligible participants will receive blinded treatment, GB0139 or placebo, for 52 weeks. Clinic visits will be performed at week 0/baseline, and then at weeks 4, 8, 12, 26, 40, and 52 according to the Study Time and Events Table (Section 2.2)

Follow up Period - At the end of the treatment period (week 52), a safety follow-up phone call will be performed 7 days after the withdrawal/last study visit.

## 6.2 Number of Participants

Approximately 141 participants in total will be randomized in GALACTIC-1.

Participants are considered evaluable if they have taken at least one dose of the double-blind treatment.

Participants who prematurely discontinue double-blind study treatment after randomization can remain in the study and complete the remaining scheduled visits, if possible.

Any participants who withdrawn from the study after randomization cannot be replaced and re-screened.

## 6.3 Participant - and Study completion

A participant is considered to have completed the study if he/she has completed all periods of the study including follow up visit.

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

## 6.4 Study Design Rationale

Based on the DSMB’s recommendation, GALACTIC-1 can continue to randomise participants with IPF to receive either placebo or 3 mg GB0139 in a randomized and blinded fashion.

A placebo treatment arm included in the study is to allow for a quantitative assessment of the efficacy of 3 mg GB0139 compared with an inactive control. Use of the placebo is also essential in the evaluation of the GB0139 safety in this study.

DSMB also recommended no further co-administration of GB0139 with nintedanib and pirfenidone. Therefore, patients who are not currently taking or cannot tolerate nintedanib or pirfenidone will be eligible for screening (Section 7.0). Furthermore, nintedanib and pirfenidone are defined as study prohibited medications in Protocol version 6.1_UK.

Eligible participants will be randomized in a ratio of 2:1 to receive either 3 mg GB0139 or placebo. The updated design has maintained the ratio of active to placebo in the original study design, after the 10 mg GB0139 treatment group was removed in Protocol version 6.1_UK.

The 12 months (52 weeks) treatment duration is considered optimal for evaluating the primary endpoint in the study.

FVC is generally accepted as a measure of disease severity and as a predictor of survival in IPF. FVC is also commonly used as the primary efficacy measure for clinical trials in IPF. The decline of lung function in IPF is punctuated by acute exacerbations which carry a substantial risk of hospitalization and mortality. Thus, any intervention which reduces the time to exacerbation represents a substantial benefit and will be evaluated. In addition to measurements of lung volume (FVC), diffusion capacity for carbon monoxide (DLCO) as well as oxygen saturation (SpO2) will be monitored and assessed as secondary lung function endpoints.

Survival is recognised as an important measure to evaluate effect of a potential treatment for IPF therefore, time to death (all-cause mortality) is included as one of the key secondary endpoints. Patients with IPF also suffer from dyspnea, cough and poor exercise tolerance, which can reduce the quality of life and cause a severe restriction in their activities of in every-day life. Therefore, a number of patient-reported outcome instruments including SGRQ will be used to document the effect on symptoms and their impact on the patient’s quality of life.

### 6.5 Dose Justification

In the phase Ib study in IPF patients 3 mg GB0139 administered via dry powder inhaler has shown to reduce alveolar macrophage (AM) Gal-3 surface expression to 42.8 % of baseline levels over 14 days of treatment [50]. When comparing the 3 mg GB0139 group with placebo on day 14, five high relevance plasma markers (PDGF-BB, PDGF-AA, PAI-1, YKL-40 and MCP 1) associated with IPF pathogenesis were either significantly reduced or showed a trend for reduction [50]. In addition, there was a correlation between the change in lung Gal-3 levels and the change in plasma levels of the high relevance biomarkers across the 3 mg and 10 mg groups (see IB for details). Therefore, these reductions in plasma biomarkers were associated with the GB0139-induced reduction in Gal-3 expression on AMs and support the lung PK/PD as the key driver of the observed systemic biomarker changes. These observations, coupled with AM Gal-3 target engagement data on 3 mg GB0139, indicated potential efficacy at this dose level in IPF which supports the further evaluation of 3 mg in the present study.

The 3 mg GB0139 dose was also well tolerated in healthy participants and participants with IPF in the phase I study.

### 6.6 Dosing

Following Protocol version 6.1_UK, subjects eligible for the study will be randomised into 2:1 ratio to one of two treatment arms:

A. GB0139 3mg once a day (2x 1.5mg capsules) by inhalation

B. Placebo once a day (2x placebo capsules) by inhalation

## 7.0 STUDY POPULATION

Prospective approval of protocol deviations to enrolment criteria, also known as protocol waivers, is not permitted.

### 7.1 Inclusion Criteria

Each subject must meet all of the following inclusion criteria in order to be enrolled in the study/ randomized to treatment:

1. Male and female subjects aged ≥ 40 years of age with a diagnosis of IPF established during the previous five years according to ATS/ERS/Fleischner criteria [1-3]. A diagnostic HRCT scan assessed according to the ATS/ERS/Fleischner criteria should be available from within the 12 months (up to 12 months + 27 days) prior to screening. Note: a separate HRCT scan will *not* be performed as part of the study. Diagnostic HRCTs will be subject to central reading for assessing study eligibility.
2. Lung function parameters as follows:
    a. FVC > 45% of the predicted value at screening
    b. DLCO (corrected for Hb) of 30% to 79% of the predicted value at screening.
3. Participants who currently are not being treated with nintedanib or pirfenidone; or cannot tolerate nintedanib or pirfenidone.
4. Subjects must sign and date a written, IRB/EC approved informed consent form and any required authorization prior to initiation of any study procedures.

## 7.2 Exclusion Criteria

Subjects meeting any of the following exclusion criteria are not to be enrolled in the study/randomized to treatment:

1. Currently has significant airways obstruction: FEV1/FVC ratio of < 0.7 at screening.
2. Has clinical evidence of active infection, including, but not limited to, bronchitis, pneumonia, sinusitis, urinary tract infection, and cellulitis.
3. Has a history of malignancy within the last 2 years with the exception of basal cell carcinoma, squamous cell carcinoma of the skin (localised, treated or cured), chronic lymphocytic leukaemia (under observation) and prostate cancer requiring anti-androgens, localised treatment (minor surgery, radiotherapy) and/or managed by observation.
4. Has any condition other than IPF that, in the opinion of the investigator, is likely to result in the death of the subject within the next 2 years.

5. Presence of other disease that may interfere with testing procedures or in the judgement of the Investigator may interfere with trial participation or may put the patient at risk when participating in this trial.
6. Is likely to receive lung transplantation within the next 12 months.
7. Currently receiving nintedanib, pirfenidone, high dose corticosteroid, cytotoxic (e.g., chlorambucil, azathioprine, cyclophosphamide, methotrexate), vasodilator therapy for pulmonary hypertension (e.g., bosentan), also see prohibited medications (Section 8.3.2). A current dose of less than or equal to 15 mg/day of prednisone or its equivalent is acceptable if the dose is anticipated to remain stable during the study.
8. Prior use of GB0139 or previously randomized in GALACTIC-1.
9. Prior use of nintedanib or pirfenidone within 7 days of initiation of screening.
10. Prior use of investigational drugs within 30 days (or 5 half-lives, whichever is longer) of initiation of screening.
11. Participating in another interventional clinical trial.
12. Has a history of unstable or deteriorating cardiac or pulmonary disease (other than IPF) within the previous six months, including, but not limited to, the following:
    a. Unstable angina pectoris or myocardial infarction, or percutaneous coronary intervention within the last 6 months.
    b. Congestive heart failure requiring hospitalization.
    c. Uncontrolled clinically significant arrhythmias.
13. If female, the subject is pregnant or lactating or intending to become pregnant before participating in this study during the study and within 33 days after last dose of the study drug; or intending to donate ova during such time period.
14. Woman considered to be of childbearing potential who do not use highly effective birth control methods (A/B/C) during the study and for 33 days after last administration of study drug. Female subjects will be considered to be of childbearing potential unless surgically

sterilised by hysterectomy or bilateral tubal ligation, or postmenopausal for at least 12 months.

A. Highly effective methods of birth control (when used consistently and correctly) are:

- intrauterine device (IUD) placed at least 4 weeks prior to the IMP administration
- bilateral tubal occlusion.
- vasectomised partner[B].
- sexual abstinence[C].
- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, transdermal.
- progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, implantable.
- intrauterine hormone-releasing system (IUS).

B. Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential trial subject and that the vasectomised partner has received medical assessment of the surgical success.

C. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial.

15. Male partners of women of child bearing potential not committing to using condoms during the course of the study and 90 days after last administration of study drug, unless they have undergone male sterilization (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).

16. Hypersensitivity to the active substance (GB0139) or the excipient (lactose).

# 8.0 STUDY DRUG

## 8.1 Study Drug Administration

Both GB0139 (3 mg) as well as the placebo will be administered via inhalation once a day using the Plastiape RS01 Monodose DPI device (a CE marked device).

All subjects must be trained in the use of the inhaler device at w0/baseline, according to the instructions provided with the device (Appendix 1 in Section 18.0). Placebo capsules and inhaler devices will be provided for training and demonstration purposes. Site staff should be assured the subject will be able to administer the drug at home safely and competently. The same DPI devices can be used for training throughout the study but must not be used for dosing. Study site personnel will dispense the IMPs, and site personnel will facilitate administration when the subject is in the clinic, at the time of w0/baseline, however subjects themselves will hold the DPI device during inhalation. At subsequent visits up until study completion/withdrawal the subject's technique with the DPI device should be assessed to ensure correct usage and further instruction given if required/requested.

Capsules will be loaded into the DPI device as per the instructions provided with the device (and included in Appendix 1). A single device will be used per two weeks of dosing. The device will be dispensed with the IMP. One (1) to three (3) inhalations from the DPI device will be performed with each capsule. Any problems with drug administration will be noted in the CRF.

Site staff will instruct the subject on how to take the drug, including the number of capsules to be inhaled each day and the timing of dose administration. On administration of the first dose the subject should be monitored at the site for 1 hour to observe any acute adverse reaction to study medication (e.g., bronchospasm). The PI/attending physician may perform additional spirometry as part of their assessment if, in their opinion, it is safe to do so and would be helpful in the assessment of any such events. For daily doses taken at home, subjects should be advised to administer the study drug at approximately the same time of day. Subjects will be given DPI devices and enough supplies until their next visit (plus one week). Subjects will be encouraged to contact the site for additional advice and support if they have an issue whilst using the inhaler.

Subjects will also be instructed to bring back unused medication. All used and unused blister should be returned to site for accountability purposes. Individual used capsules can be discarded by the participant at home.

## 8.2 Permitted medications

Vaccines that are available to study participants including but not limited to COVID-19, influenza and pneumonia vaccines.

## 8.3 Prohibited Medications including approved and non-approved medications for IPF

### 8.3.1 Medications approved for IPF

- Nintedanib
- Pirfenidone

Following the most recent DSMB recommendation, the above approved medications for IPF are prohibited in GALACTIC-1, and if taken, should result in immediate exclusion from screening for the study, or withdrawal from the study treatment.

Under caring physician's medical judgement, if deemed appropriate, patients with IPF may discontinue nintedanib or pirfenidone and be considered for screening after a wash out period of minimum 7 days.

Following randomization, study participants are only permitted to take nintedanib or pirfenidone after withdrawals of the inhaled study treatment.

### 8.3.2 Non-approved medications for IPF

Current guidelines recommend against use of a number of drugs, either alone or in combination, to modify disease progression in idiopathic pulmonary fibrosis, and the use of the following should be result in exclusion from the study:

- N-acetylcysteine
- Azathioprine
- Ambrisentan

- Bosentan
- Macitentan
- Mycophenolate mofetil
- Warfarin (disallowed only when prescribed solely for the treatment of IPF and is permitted for other recognised indications such as Atrial Fibrillation)

## 8.4 Management of Clinical Events

Management of all types of adverse events, regardless of the possible underlying cause is the responsibility of the treating physician/investigator.

## 8.5 Blinding and Unblinding procedures

### 8.5.1 Blinding

This study is a double-blind study which will be maintained throughout the study, including the follow-up period. Study medication is identified by a medication code number. Packaging and labelling will be otherwise identical. Subjects, Investigators and everyone involved in analysing or with an interest in this double- blind study (Sites, Study team, CROs, other service providers) will remain blinded with regard to the randomised treatment assignments until after database lock. Only the DSMB will have access to unblinded information. An IVRS/IWRS will be used to assign subjects to treatment groups at study start. The randomisation code will be kept undisclosed up to database lock.

### 8.5.2 Unblinding

If the Investigator believes that knowledge of the IMP received by a subject is essential for appropriate treatment of an AE, the Investigator should ideally consult with the CRO/Galecto before breaking the code. In any event, the Investigator should inform Galecto Biotech AB (subsequently referred to as Galecto) as soon as possible whenever the code has been broken for a subject. In the event that the site requires emergency access to an individual subject code and personnel from Galecto are not available, each site may break the blind without any prior consultation. In such an event, the Chief Investigator, Principal Investigator or delegate would

notify Galecto as soon as possible *via* email or fax. If the Investigator needs to break the blind for an individual subject, the date and reason will be recorded in the subject's CRF. The IVRS/IWRS will provide a telephone/web procedure for unblinding the code to the Investigator / Pharmacist / investigational drug storage Manager. The Investigator will not reveal the unblinded treatment code to any other member of the clinical team involved in the study or to the Study Monitor. If the code is broken for any individual subject, the subject will be withdrawn from the study and the procedures accompanying the withdrawal visit performed. If the code is broken without justification, this will be deemed a serious protocol violation.

To avoid unblinding of the study team through drug safety reports which are to be unblinded as per regulatory requirements, a procedure will be maintained to keep code-breaking in these cases unknown to the study team.

### 8.6 Description of Investigational Agents

The planned dose levels (3 and 10 mg GB0139) have been selected in the original study design (Protocol version 5.1_UK) following review of non-clinical pharmacokinetic, safety pharmacology and toxicology data. Pharmacokinetic, toxicokinetic and toxicology studies in mice, rats and dogs indicate the drug is readily bioavailable via the inhaled route with little or no accumulation after 14-day dosing and is excreted in the faeces with a t1/2 of approximately 6 h.

Given the lack of adverse effects seen in the two species as well as the favourable safety profile seen in the phase I/IIa in healthy volunteers and IPF subjects, no direct anticipated adverse drug specific side effects are expected in the current study, nor are any drug interactions anticipated given the clear cytochrome profiling. Further details regarding non-clinical pharmacokinetic, safety pharmacology and toxicology data can be found in the IB.

### 8.7 Packaging and Labeling

The IMPs will be prepared by the sponsor and supplied to the Investigator. The Sponsor must ensure that the Investigator is notified prior to dispatch of IMP supplies, and of the anticipated date of their arrival. The IMP is shipped upon first screening, then arrives on site prior to dosing.

The IMPs must be received at each Investigational site by a designated person, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated staff have access. After a review of the temperature monitors included with shipments the Sponsor/CRO must ensure that it is confirmed that the transportation conditions were acceptable.

### 8.8 Storage, Handling, and Accountability

Following the Sponsor's approval, all remaining IMP will either be returned to the Sponsor or sent for destruction within 8 weeks of completion of the study-dosing period.

All used IMP containers and unused IMP will be held under quarantine in the investigator site facility pending accountability/return/destruction.

# 9.0 STUDY END POINTS

## 9.1 Primary Endpoint

- The annual rate of decline in Forced Vital Capacity (FVC; expressed in mL over 52 weeks).

## 9.2 Key Secondary Endpoints

- Proportion of subjects with an absolute decline from baseline in FVC (% pred) of ≤10% at Week 52.
- Change from baseline in SGRQ total score at Week 52.
- Time to first hospitalization (respiratory related, including acute exacerbation of IPF).
- Time to death (all-causes).

## 9.3 Secondary endpoints

- Proportion of subjects with an absolute decline from baseline in FVC % pred of ≤5% at w52.
- 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 dyspnoea 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.
- Time to initiation of nintedanib or pirfenidone.
- Change in FVC expressed in mL over 52 weeks for subjects who have never been treated with pirfenidone or nintedanib.

## 9.4 Safety Endpoints

- The following measure of safety will be assessing throughout the study:
  - Vital signs
  - Physical examination
  - Weight
  - Clinical laboratory tests (haematology, clinical chemistry and urinalysis)
  - Adverse events (see Section 11.0)
  - 12-lead electrocardiogram (ECG)

## 9.5 Exploratory Endpoints

### 9.5.1 Biomarkers

Change from baseline in selected biomarkers including but not limited to: YKL 40, PAI 1, PDGF-BB, MCP-1, CCL-18, KL-6, CA-125, CA-19, Gal-3 and collagen neoepitopes – described in Appendix 2 (Section 18.0) – over time up to week 52 in all subjects.

### 9.5.2 Initiation or termination of nintedanib and pirfenidone in the previous stratified study population

### 9.5.3 Time to initiation of pirfenidone or nintedanib treatment for SoC2 participants up to the time when SoC1 and SoC2 were removed in the study.Pharmacogenetics

The study includes a pharmacogenetic component including but not limited to analysis of GAL-3 and IPF disease related genes of interest that might relate to the efficacy and/or safety of GB0139.

## 10.0 STUDY CONDUCT

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

### 10.1 Study Personnel and Organizations

The contact information for the project clinician for this study, the clinical laboratories, the coordinating investigator for each member state/country, the interactive voice response system (IVRS)/interactive web response system (IWRS) provider, the contract research organization (CRO) team may be found in the Investigator Site File. A full list of investigators is available in the sponsor's investigator database.

### 10.2 Arrangements for Recruitment of Subjects

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice/hospital or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/independent ethics committee (IEC).

Enrollment strategies for this study may include the following:

- Review of local practice/hospital database
- Communication with other physicians/colleagues and cooperating health care facilities that regularly refer subjects for further diagnosis and care

### 10.3 Visit schedule

There is a screening visit and 7 study visits planned over the 52 weeks treatment period. A safety follow up will be conducted via phone 7 days after the final visit.

#### 10.3.1 Screening & Randomisation

After giving his/her Informed Consent, the patient may be selected based on inclusion and exclusion criteria for the study at visit 1. The shipment or transfer of HRCT for review can be

organised before the screening visit provided the participant has given and signed his Informed Consent. The screening is up to 6 weeks.

The participants will be randomised at visit 2 if all inclusion and exclusion criteria are fulfilled. The results of laboratory parameters from visit 2 may only become available 24 to 72 hours after visit 2. Therefore, laboratory results from visit 2 cannot qualify as exclusion criteria. However, in case these results would retrospectively fulfil an exclusion criterion, the patient will be withdrawn unless continuation is justified in writing by the Investigator.

### 10.3.2 Re-screening visit

If a subject fails to meet the screening criteria for reasons which the Principal Investigator judges to be anomalous or the result of a temporary factor, those test(s) may be repeated once at an ad hoc visit(s), providing the subjects is still within the six weeks screening window. Subjects who fail screening and are outside the six weeks screening window, whom the Principal Investigator judges to now meet the screening criteria will be permitted to undergo rescreening one additional time, with advanced approval from Syneos Health Medical Monitors.

If a re-screening visit occurs within 12 weeks of initial screening it is not required to repeat PFT and DLCO, if the PFT and DLCO measured at the initial screening have met study inclusion criteria.

### 10.3.3 Treatment period

There will be seven study visits during the treatment period as follows: at randomization/baseline (w0), w4, w8, w12, w26, w40, and w52. Details for the data collected at each visit are given in the time and events table (Section 2.2). 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.

#### 10.3.3.1 *Participants randomized prior to Protocol version 6.1_UK and eligible to continue participation*

Participants who were already randomised and eligible to remain in GALACTIC-1 and continue to receive blinded study treatment (3 mg GB0139 or placebo) should attend visits as required by

Protocol version 5.1_UK until Protocol version 6.1_UK is approved. Once the amended ICF is approved they should be re-consented. Participants who have completed w52 visit by the time the Protocol version 6.1_UK is approved should attend a withdrawal visit as soon as possible followed by a phone call follow up as specified in the Protocol version 6.1_UK.

### 10.3.4 Study treatment completion and Follow-up period

Subjects will be considered to have completed the study treatment period if assessments according to the protocol at week 52 have been performed. At the end of the treatment period subjects will enter a follow-up period. Follow-up phone call can be performed from 7 days and up to 14 days after the last study visit or withdrawal visit.

Additional individual visits may be scheduled by the treating physician on a case by case basis. Data collected at these visits will be recorded as unscheduled visits in the eCRF.

At all scheduled visits, study site staff will collect treatment patterns and outcomes, vital status, clinical events, AE/SAE data from the charts of study subjects followed at the participating sites.

## 10.4 Study procedures

### 10.4.1 Data collection

An electronic case report form (eCRF) system will be utilized for data collection, monitoring, and quality control. Data validation will be programmed in the eCRF system to automate data queries. The physician or assigned study personnel will complete the eCRFs at every visit, and as required by the protocol.

If clarifications are needed, queries will be raised either by the monitor of the study or the assigned data management team, through the built-in query management functionality in the eCRF. The physician or assigned study personnel will be required to respond to these queries through the eCRF system.

Subject data collected on eCRFs during the study will be recorded in an anonymous fashion to ensure subject confidentiality. The physician must maintain source documents where relevant for

each subject in the study, consisting of all demographic and medical information, and keep the written informed consent form. All information on the eCRFs must be traceable to these source documents in the subject's medical file.

Initiation of the participating sites will be performed by the designated CROs. Before study initiation, a CRO representative will review the protocol, the CRF and the eCRF system with the physicians and their staff. CROs will follow streamlined SOPs that have been reviewed and approved by Galecto.

Concomitant or prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

### 10.4.2 Informed Consent

Each subject must provide written informed consent before any study-required procedures are conducted, and before the diagnostic HRCT can be sent for central review.

### 10.4.3 Subject Demographics

Subject demographics will be collected at screening visit 1.

- Age at baseline
- Gender
- Height and body weight (for BMI computation)

### 10.4.4 Medical History

During the Screening period, a complete medical history will be compiled for each subject. The following variables will be collected:

- Smoking history, recorded in pack-years
- Pre-existing conditions

- Time of IPF diagnosis by HRCT or surgical lung biopsy
- Time of start of treatment with pirfenidone or nintedanib (as appropriate)
- Time point and reason for discontinuation of treatment with pirfenidone or nintedanib (as appropriate)
- Any episode of acute exacerbation in the subject's IPF context during three months prior to randomization
- Any medication used prior to screening including vaccinations

### 10.4.5 Physical Examination

A physical examination will be completed as per standard of care at all visits.

### 10.4.6 Vital Signs

Vital sign measurements include supine (after at least 5 minutes in this position) measurements of diastolic and systolic blood pressure, heart rate, and body temperature. They will be conducted at all visits.

### 10.4.7 Health-related Quality of Life Questionnaires

Three patient-reported assessments related to symptoms and quality of life will be collected during the study. A version of each will be to the site and will be completed by each subject at the visits as per the T&E table Section 2.2

- St George's Respiratory Questionnaire (SGRQ) a validated QoL for IPF
- The Short Form Health-36 survey
- The University of California San Diego, shortness of breath questionnaire (UCSD-SOBQ)

### 10.4.8 12-Lead Electrocardiogram

Safety monitoring by ECG will be performed using site local equipment. PR interval, QRS duration, QT interval and QTcF are required to be evaluated.

### 10.4.9 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed by a central laboratory as outlined below. Blood samples for analysis of the clinical chemistry and hematological parameters, urinalysis and biomarkers are shown in Table 2, Table 3 and Table 4.

**Table 2: Clinical Chemistry and Hematology Tests**

| Hematology | Serum Chemistry | |
|---|---|---|
| Hematocrit | Albumin | Glucose |
| Hemoglobin | Alkaline phosphatase (ALP) | Potassium |
| Leukocytes with differential count | Aspartate transaminase (AST) | Sodium |
| Platelet (count) | Alanine transaminase (ALT) | |
| | Bilirubin (total) | |
| | Calcium | |
| | Creatinine | |

**Table 3: Clinical Urinalysis Tests**

| Urinalysis | |
|---|---|
| Bilirubin | pH |
| Glucose | Protein |
| Ketones | Specific gravity |
| Leukocytes | Turbidity and color |
| Nitrite | Urobilinogen |
| Occult blood | |

Results are recorded qualitatively as: -, +, ++, +++

### 10.4.10 Pregnancy Test

A serum pregnancy (choriogonadotropin beta) test will be completed by all females of child-bearing potential during screening; this test must be negative for the subject to be enrolled. Urinary pregnancy tests will then be repeated at various times during the study as specified in the Time & Events table.

Any occurrence of a pregnancy in a subject undergoing treatment in the GALACTIC-1 study must be reported according to the rules agreed upon with the designated CRO within 24 hours of learning of its occurrence. The pregnancy should be followed-up via fax or email to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or new-born complications.

Pregnancy should be recorded on a *Pharmacovigilance Pregnancy Form* and reported by the treating physician or other involved health care professional to Galecto's Pharmacovigilance (PV) representative. In case of any congenital abnormality, birth defect or maternal and new-born complications, the possible relationship to the Galecto drug should be reported.

Additionally, any SAE experienced during pregnancy must be reported into the eCRF system.

Note: should the eCRF system become non-operational, the site must complete the appropriate paper *Serious Adverse Event Form*. The completed form is then faxed/mailed within 24 hours of the Investigator's or site's awareness; however, the reported information must be entered into the eCRF system once it becomes operational. Please see Section 11.2 for PV reporting information.

### 10.4.11 Biomarkers

A serum sample for the assessment of biomarkers will be collected at baseline (visit 2) and weeks 4, 12, 26 and 52. The list in Table 4 gives *examples* of biomarkers potentially related to Galectin-3 activity and/or IPF disease severity/prognosis. More detail on the rationale for including such biomarkers is described in Appendix 2 (Section 18.0). Ultimately, individual biomarkers may be added to or removed from this list.

**Table 4: Biomarker Panel**

| Serum Biomarkers | |
|---|---|
| Gal-3 | KL-6 |
| Collagen neoepitopes | PAI-1 |
| YKL-40 | PDGF-BB |
| MCP-1 | CCL-18 |
| CA-125 | CA-19 |

### 10.4.12 Genetics Sample

All subjects will be asked for a blood sample for genetic assessment. However, this is not mandatory for the subject to participate in the study. A single sample will be taken at visit 2 or at any visit throughout the study and processed or stored after separate informed consent is given in accordance with local ethical and regulatory requirements. The sample will be anonymised, meaning there will be no way to trace back to the identity of the donor. Samples will be stored for up to 15 years after the end of the study or until there is no more material available for tests.

### 10.4.13 Spirometry

Equipment and manual will be provided by Clario (previously ERT). Data will be centrally evaluated by Clario.

### 10.4.14 Pulse Oximetry

Pulse oximetry will be measured using sites local equipment.

### 10.4.15 DLCO

Sites use local equipment to measure DLCO using a manual provided by Clario. Data will be centrally overread by Clario.

### 10.4.16 6MWT

Test manual will be provided by Clario.

### 10.4.17HRCT central overread

HRCT will be reviewed by an independent Chest radiologist, assigned byClario, who will assess according to the ATS/ERS/Fleischner criteria [1-3].

### 10.4.18 Concomitant Medications and Procedures

Medications including vaccination used by the subject will be recorded in the electronic case report form (eCRF) to cover screening period and then prospectively at all study visits (treatment and follow up periods) until study completion/withdrawal. See Section 8.3.2 for a list of medications and therapies that are prohibited during the study.

### 10.4.19 Adverse Events

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the Time and Events Table (Section 2.2). Refer to Section 11.0 for details regarding definitions, documentation, and reporting of pretreatment events (PTEs), AEs, and SAEs.

## 10.5 Discontinuation of study treatment

Temporary discontinuation of GB0139 for <2 weeks will be permitted, if for reasons other than those stated below. The reason for discontinuation should be documented in the eCRF.

Treatment with study drug may be permanently discontinued for any of the following reasons:

- Persistent non-adherence by subject
- Adverse event assigned to the investigational drug
- Overall unsatisfactory therapeutic response
- Study terminated by sponsor
- Withdrawal by subject
- Lost to follow-up
- Other (cause to be elaborated on in the subject's file)

In all cases, participants should be encouraged to discuss any potential study treatment discontinuation with the investigator prior to stopping treatment. If considered medically appropriate by the PI, participants who have been withdrawn from study treatment can remain in the study, resume their usual standard of care treatment for IPF, if applicable, and complete scheduled visits and study assessments up to the follow up phone call.

## 10.6 Withdrawal of Subjects from the Study

Subjects may withdraw for the following reasons:

- Lost to follow-up
- Study terminated by sponsor
- Withdrawal by subject
- Completed study
- Death
- Lung transplant
- Other (cause to be elaborated on in the subject's file)

All study procedures outlined for the withdrawal visit will be completed as specified in the Time and Events Table (Section 2.2). The primary reason for study drug discontinuation will be recorded on the eCRF.

Following the study withdrawal, no new information will be collected from the withdrawn subject and added to the existing data or any database.

## 10.7 Study Compliance

Study drug will be administered or dispensed only to eligible subjects under the supervision of the investigator or identified sub-investigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

# 11.0 ADVERSE EVENTS

## 11.1 Definitions

### 11.1.1 Pretreatment Event Definition

A pretreatment event (PTE) is any untoward medical occurrence in a subject who has signed informed consent to participate in a study but before administration of the first dose of study medication; it does not necessarily have to have a causal relationship with study participation.

### 11.1.2 Treatment Emergent Adverse Event

A treatment emergent adverse event (TEAE) is any untoward medical occurrence that emerges during treatment, having been absent pre-treatment or worsens relative to the pre-treatment state.

### 11.1.3 Adverse Event Definition

Adverse Event (AE) means any untoward medical occurrence in a subject or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

### 11.1.4 Serious Adverse Event Definition

Serious Adverse Event (SAE) means any untoward medical occurrence that at any dose:

- Results in **death.**

- Is **life-threatening** (refers to an AE in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires subject **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph in Section 11.2 on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**?
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the subject, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on subject/event outcome or action criteria described above and is usually associated with events that pose a threat to a subject's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/$mm^3$ to less than 2000 is considered Grade 3 (severe)

but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

## 11.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events

All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 11.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs and serious pretreatment events (as defined in Section 11.1) must be reported (see Section 11.3 for the period of observation) by the investigator to Galecto's pharmacovigilance representative or designee (contact information provided below). This should be done by faxing/mailing the paper SAE Form within 24 hours after becoming aware of the event before recording the SAE into the eCRF system. Follow-up information on the SAE or serious pretreatment event may be requested by Galecto. SAE report information must be consistent with the data provided on the eCRF. The SAE Form, created specifically by Galecto (or by the designated CRO), will be provided to each clinical study site.

### 11.2.1 SAE Reporting Contact Information:

E-mail: [redacted]

Fax number:

| Country | Toll-Free Fax No. |
|---|---|
| INDIA | [redacted] |

Planned hospital admissions or surgical procedures for an illness or disease that existed before the subject was enrolled in the trial *or* before study drug was given are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g. surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the severity (toxicity grade) of the event and the relationship of the event to study drug administration. For serious pretreatment events, the investigator must determine both the severity (toxicity grade) of the event and the causality of the event in relation to study procedures.

**Relationship** of the event to study drug administration (i.e., its causality) will be determined by the investigator responding yes (related) or no (unrelated) to this question: “Is there a reasonable possibility that the AE is associated with the study drug?”

### 11.3 Monitoring of Adverse Events and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from the signing of informed consent through 30 days after administration of the last dose of study drug and recorded in the eCRFs.
- SAEs.
- Serious pretreatment events will be reported to the Galecto pharmacovigilance representative or designee from the time of the signing of the informed consent form up to first dose of study drug and will also be recorded in the eCRF.
- Related and unrelated treatment-emergent SAEs will be reported to the Galecto pharmacovigilance representative or designee from the first dose of study drug through 30 days after administration of the last dose of study drug and recorded in the eCRF. After this period, only related SAEs must be reported to the Galecto pharmacovigilance representative or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es).

### 11.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Galecto pharmacovigilance representative or designee (see Section 11.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male subject becomes pregnant during the male subject's participation in this study, the sponsor must also be contacted immediately by emailing a completed Pregnancy Form to the Galecto pharmacovigilance representative or designee (see Section 11.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

## 11.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately report this via the phone numbers or e-mail addresses provided below.

A medication error is a preventable event that involves an identifiable subject and that leads to inappropriate medication use, which may result in subject harm. Whereas overdoses and underdoses constitute medication errors, doses missed inadvertently by a subject do not. Individuals who identify a potential medication error (including overdose) situation should immediately report this via the phone numbers or e-mail addresses provided in Section 11.2.1.

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to IQVIA (refer to Section 11.2).

## 11.6 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

A designated CRO will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency (EMA), investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as an expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the trial. The investigational sites will also forward a copy of all expedited reports to their IRB or IEC in accordance with national regulations.

# 12.0 SAFETY MONITORING

## 12.1 Data and Safety Monitoring Board (DSMB)

An independent Data and Safety Monitoring Board (DSMB) will be implemented. Members of the DSMB selected and appointed by the sponsor will be fully independent of any ties to the trial, the sponsor, or any other activity or entity that might affect their objectivity. The establishment and management of the DSMB is prescribed by a charter and provides reports to the study team, sponsor, CRO. The minutes of all DSMB meetings will be stored in the Trial Master File (TMF).

The DSMB will continue to conduct regular review of the trial safety data, with the focus on the following safety information:

• Death cases

• Serious adverse events

• Adverse events leading to withdrawal from study

The DSMB will recommend continuing, modifying or stopping the study based on these reviews. The DSMB is committed to meet and to make timely decisions. The DSMB will inform the coordinating Investigator of the trial, the Sponsor, and the Trial team if any urgent decision has to be implemented.

## 12.2 Event Adjudication

Following study read-out, Galecto may decide to employ an independent adjudication panel to review, in a blinded manner, events reported in the study including but not limited to all cases of death (the primary cause of death) and reported acute IPF exacerbations (based on written clinical reports, for diagnostic confirmation). See Appendix 3 (Section 18.0) for a definition of acute exacerbation in IPF.

## 13.0 DATA HANDLING AND RECORD KEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. If selected for coding, AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

### 13.1 eCRFs

The designated CRO will supply investigative sites with access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. The data collection forms are used to transmit the information collected to ensure quality and performance of this study to the sponsor, CRO partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent data, missing data, and questionable values. Queries may be issued by the CRO personnel and will be answered by the site. Issues will be reconciled with Galecto.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any

form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

### 13.2 Record Retention

The investigator agrees to keep the records stipulated in Section 13.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. No study document is to be destroyed without prior written agreement between Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor in writing of the new responsible person and/or the new location.

## 14.0 STATISTICAL METHODS

As part of Protocol version 6.1_UK study design and objectives have been amended to focus on comparisons between GB0139 3 mg and Placebo within the SoC2 strata (participants not currently treated with pirfenidone or nintedanib). All relevant subsections within this section have been amended accordingly.

### 14.1 Statistical and Analytical Plans

A blinded data review will be conducted prior to database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

For descriptive statistics categorical data will be presented as frequencies and percentages. Percentages will be based on the number of subjects with non-missing values for the corresponding categorical variable. Continuous data will be presented as number of subjects with non-missing values, mean standard deviation, median, minimum and maximum, as well as the $25^{th}$ and $75^{th}$ percentile.

All statistical tests as well as the confidence intervals will be two-sided. The study-wise type I error probability for the confirmatory analyses is set to 10%. 90% confidence intervals are to be calculated, if feasible.

Covariates for the primary analyses will be pre-specified. For secondary analyses these are anticipated to be broadly similar to primary analysis but will be fully specified in the Statistical Analysis Plan (SAP).

### 14.2 Statistical Hypothesis

The primary efficacy analyses are based on data from SoC2 only.

### 14.2.1 Primary efficacy endpoints

The superiority of GB0139 3 mg compared to Placebo (Plc) will be tested for the annual rate of decline in FVC in mL.

The null hypothesis is:

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

The alternative hypotheses are:

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

### 14.2.2 Key Secondary Efficacy Endpoints:

The superiority of GB0139 3 mg compared to Plc will be tested for the proportion of subjects with a decline ≤10% from baseline in predicted %FVC at week 52. The superiority of GB0139 3 mg compared to Plc will be tested for the change from baseline in SGRQ total score at Week 52.The superiority of GB0139 3 mg compared to Plc will be tested for the time to first hospitalization (any respiratory related, including acute exacerbation of IPF) during treatment. The superiority of GB0139 3 mg compared to Plc will be tested for time to death from all causes from date of randomization where time to death will be death at any time up to Week 52.

## 14.3 Analysis Sets

The following analysis sets will be used in this trial

- *Intention-to-Treat (ITT) Analysis Dataset* - this includes all randomized subjects
- *Modified Intention-to-Treat Analysis Dataset (mITT)* - this includes all randomized subjects with at least one application of study drug, and will be grouped according to the treatment they were randomised to.
- *Safety Analysis Dataset*- this includes all randomized subjects with at least one application of study drug, and will be grouped according to the treatment they received.

- *Per-Protocol Analysis Dataset* - this includes a subset of the subjects in the ITT analysis set 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 who took at least 80% of study intervention treatment for at least 80% of the initial 52 weeks).

## 14.4 Primary Efficacy Analysis

The primary efficacy analysis will be based on data from SoC2 only.

### 14.4.1 Analysis of Primary Efficacy Endpoint

The primary endpoint is described in Section 9.1. The primary efficacy analysis is a random coefficient regression (random slopes and intercepts) model. Treatment and baseline FVC (mL) will be included as a covariate in the analysis model. Other covariates such as age, and gender will be included as covariates unless their inclusion violates model assumptions or impacts stability. Baseline FVC is defined as the FVC result recorded at Visit w0/baseline, unless missing in which case the latest FVC before randomization in the subject's chart result will be used.

The decrease in FVC is assumed to be linear within each subject over 52 weeks. The intercepts and slopes will be assumed to be normally distributed with arbitrary covariance matrix. The within-subject error 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.

Section 14.8 details of the approaches to handling of missing data are given.

Significance tests will be based on least-squares means; p-values and two-sided 90% confidence intervals for the difference between the treatment groups will be presented. An intent-to-treat principle will be used. Analyses will be implemented using SAS® Version 9.4 or higher. The assumptions for the primary analysis of decline in FVC will be tested; details will be provided in the SAP. The primary analysis will be based on observed data (but including retrieved drop out

measurements) and will assume remaining missing data are missing at random. The effect of missing data will be investigated using multiple imputation methods which assume that subjects who discontinue treatment will no longer benefit from it in the future. See Section 14.8 for further details of these sensitivity analyses.

Subgroup analyses will be fully specified in the SAP and will include:

- Age
- Gender
- Race
- Ethnicity
- Previous treatment with pirfenidone and/or nintedanib
- Recruitment cohort (e.g., pre- or post- DSMB cutoff, and pre- or post-Protocol version 6.1_UK)

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

Data will be summarized graphically and using summary statistics.

### 14.4.2 Analysis of Secondary Endpoints

For all secondary endpoints, an intent-to-treat principle will be used.

#### 14.4.2.1 Key Secondary Endpoints

The key secondary analysis will be based on data from SoC2 only. Data will be summarized graphically and using summary statistics. The multiplicity procedure used for the key secondary endpoints will be detailed in the SAP.

Comparisons between treatment groups regarding the binary endpoint variable based on an absolute decline from baseline in FVC % predicted of ≤10% will be performed using a logistic regression model. Treatment and baseline FVC (mL) will be included in the model along with any other covariates included in the analysis of the primary endpoint. The likelihood-ratio test will be used to test for differences between treatments. Odds ratios together with 90% confidence intervals will be used to quantify the effect of treatment, comparing GB0139 3 mg to placebo as the reference.

The change from baseline in the SGRQ total score at Week 52 will be analysed using a mixed model repeated measures with covariates treatment, baseline total score along with any other covariates included in the analysis of the primary endpoint.

The time to first hospitalization (respiratory related, including acute exacerbation of IPF) will be analysed using a Cox proportional hazards model with covariates treatment, baseline FVC (mL) along with any other covariates included in the analysis of the primary endpoint. The equality of the hazard rates between the GB0139 3 mg and placebo group will be tested by the Wald test for the treatment effect. The model will include treatment as covariates. Breslow's method for handling ties will be used. Kaplan-Meier plots by treatment group will also be presented.

Time to death from all causes (plus death from respiratory-related causes if numbers allow) will be analysed using a Cox proportional hazards model. The equality of the hazard rates between the GB0139 3 mg group and placebo will be tested by the Wald test for the treatment effect. The model will include treatment, baseline FVC (mL) as covariates along with any other covariates included in the analysis of the primary endpoint. Breslow's method for handling ties will be used. Kaplan-Meier plots by treatment group will also be presented. If the proportion of deaths is less than 5%, then only frequencies of deaths by treatment group will be provided for the key secondary endpoint of time to death and no statistical analysis will be performed.

14.4.2.2 *Other Secondary Endpoints*

All further endpoint analyses will be considered exploratory in nature.

Data will be summarized graphically and using summary statistics.

Any p-values presented for the secondary endpoints will be considered nominal in nature and no adjustment for multiplicity will be made.

Further details are given in the SAP.

## 14.5 Secondary Efficacy Analysis

Secondary efficacy analysis of subgroups will be based on:

- Strata (i.e. analysing available data from SoC1)
- Previous treatment with pirfenidone and/or nintedanib
- Cohort (e.g. pre- or post- DSMB cutoff, and pre- or post-Protocol version 6.1_UK)

The same endpoints as for the primary and key secondary efficacy analysis will be analysed in an exploratory manner with the same methods as described for the primary efficacy analysis. No formal statistical hypotheses will be tested.

### 14.5.1 Other Analyses

Intervention groups should be compared on baseline characteristics, including demographics and laboratory measurements, using descriptive statistics. No inferential statistics will be used. The primary and key secondary endpoints will be analysed by age, gender, race and ethnicity. Models as described for the primary and key secondary endpoints will be used including the covariates defining the subgroup in the model and a covariate-by-treatment interaction factor. Individual subject data will be listed by treatment group and time point.

### 14.5.2 Safety Analysis

The primary assessment of benefit-risk of GB0139 3 mg compared to Plc will be based on efficacy and safety data over 52 weeks. All safety assessments described below will focus on

data collected within the first 52 weeks of the study. In addition, selected safety analyses will be repeated to include data collected beyond 52 weeks; further details will be specified in the SAP.

All treated subjects will be included in the safety analysis. The primary safety assessment will be based on the participants who received 3mg or placebo as study treatments. A separate safety assessment will be made for the participants who received study treatment in combination of nintedanib or pirfenadone. The particular tables and figures to be split in this way will be specified in the SAP. In general, safety analyses will be descriptive in nature. No hypothesis testing is planned.

Kaplan-Meier plots will be produced for the time to premature treatment discontinuation. Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. All adverse events occurring between start of treatment and end of the residual effect period will be considered ‘treatment-emergent’. The residual effect period is defined as the 28 days after the date of the last dose of trial medication. Adverse events that start before first drug intake and deteriorate under treatment will also be considered ‘treatment-emergent’. Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of MedDRA.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of subjects with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the treatment and at the end-of-treatment evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

## 14.6 Determination of Sample Size

The null hypothesis for the treatment difference between GB0139 at 3 mg and placebo for the two doses is tested using a type I error of 10% for a 2-side test. The power for detecting a statistically significant difference in the treatment effect (annual rate of decline in FVC or the FVC change from baseline to 52 weeks) is dependent on the effect size (mean treatment difference/ standard deviation) and the number of subjects per treatment group.

To detect an average difference from placebo in decline in FVC of at least 100 ml and with a standard deviation of 240 ml then a final sample size of 141 subjects would provide 75% power, assuming that future subjects are randomised into the study on a 1:2 randomisation allocation so that for every subject randomised to placebo 2 subjects will be randomised to 3 mg GB0139.

## 14.7 Randomization

Following the Protocol version 6.1_UK participants will be randomised in blocks to double-blind treatment in a 1:2 ratio (Placebo : GB0139 3 mg). The unbalanced randomisation is to maintain the same probability of allocation to placebo post-Protocol version 6.1_UK since this may impact participant enrolment. Note that prior to Protocol version 6.1_UK participants were randomized in blocks to double-blind treatment in a 1:1:1 ratio (GB0139 3 mg : GB0139 10 mg : Placebo) stratified by SoC.

The Sponsor will arrange 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 CTR. Access to the codes will be controlled and documented.

## 14.8 Handling of Missing Data

This section describes the estimands approach for the primary analysis and associated sensitivity analyses using the Detailed Clinical Objectives framework described by Bell [51].

The trial will compare GB0139 3 mg with Placebo in patients with IPF not currently treated with pirfenidone or nintedanib. The primary objective is to demonstrate superiority of GB0139 3 mg for the mean annual rate of decline in FVC in mL. A composite strategy will be taken to patient deaths with FVC attributed the lowest value recorded in the trial when a patient dies.

Three specific inter-current events (ICEs) are anticipated during the trial: death, treatment discontinuation, and initiation of pirfenidone or nintedanib. The handling of these ICEs for the treatment effect of primary interest and planned sensitivity analyses for the primary endpoint are described in Table 5.

**Table 5: Handling of anticipated ICEs for treatment effect of primary endpoint**

| **Treatment effect** | **Description** | **Death** | **Treatment discontinuation** | **Initiation of IPF therapy** |
|---|---|---|---|---|
| Primary (ICEs of treatment discontinuation or additional IPF therapy) | Randomized and treated patients with treatment policy applied for intercurrent events other than death | FVC attributed the lowest value recorded in the trial when a patient dies | Analysis will include all available FVC measurements after randomised treatment discontinuation | Analysis will include all available FVC measurements after initiation of additional IPF therapy |
| Sensitivity 1 (on-treatment) | Randomized and treated patients while on randomised treatment | FVC attributed the lowest value recorded in the trial when a patient dies | Analysis will exclude any FVC measurements after randomised treatment discontinuation | Analysis will exclude any FVC measurements after initiation of additional IPF therapy |
| Sensitivity 2 (ICE of Death) | Randomized and treated patients while on | FVC attributed value of 0 | Analysis will exclude any FVC measurements after | Analysis will exclude any FVC measurements after |

| | | | | |
|---|---|---|---|---|
| | randomised treatment | when a patient dies | randomised treatment discontinuation | initiation of additional IPF therapy |
| Sensitivity 3 (Tipping point for ICE of Death will only be performed if sensitivity 2 indicates a different conclusion to primary analysis) | Randomized and treated patients while on randomised treatment | When a patient dies FVC attributed a series of values between 0 and the lowest value recorded in the trial | Analysis will exclude any FVC measurements after randomised treatment discontinuation | Analysis will exclude any FVC measurements after initiation of additional IPF therapy |

Further details for the tipping point analysis can be found in the SAP.

# 15.0 QUALITY CONTROL AND QUALITY ASSURANCE

## 15.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be done periodically during the study to ensure that all aspects of the protocol are followed, and according to the monitoring plan. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of eCRFs and associated source documents. It is important that the investigator and delegated study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

## 15.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site must document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site must notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. Protocol Deviations are recorded by the CRO's CRA in their clinical trial

management system. All recorded Protocol Deviations will be shared with the investigator in writing following each monitoring visit, and period reports will be made available as required for submission to the EC/IRB. Recorded Protocol Deviations will also be reviewed regularly with Galecto.

The investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement from the sponsor or a prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the site as soon as possible and an approval from IRB should be obtained.

The investigator must document all protocol deviations.

### 15.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit or remote auditing. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (e.g., the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 15.1.

## 16.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual subjects (i.e., subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Section 18.0. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

### 16.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (i.e., before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (e.g., informed consent form) reviewed; and state the approval date. Once the sponsor or designee has confirmed

the adequacy of site regulatory documentation and, when applicable, the sponsor or designee has received permission from competent authority to begin the trial, it will notify investigative sites meaning that protocol activities and screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

### 16.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form describes the planned and permitted uses, transfers, and disclosures of the subject's personal health information for purposes of conducting the study. The informed consent form further explains the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the subject and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The designated CROs are responsible for the preparation, content, and IRB or IEC approval of the informed consent form. The informed consent form must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

## 16.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 16.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected on the subject's eCRF).

## 16.4 Publication, Disclosure, and Clinical Trial Registration Policy

### 16.4.1 Publication

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public

disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of Galecto.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

### 16.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Galecto will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites on or before start of study. Galecto contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

As needed Galecto and Investigator/site contact information may be made public to support subject access to trials via registries. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process.

### 16.4.3 Clinical Trial Results Disclosure

Galecto Biotech will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites (including the Galecto corporate site) and registries.

## 16.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor's

designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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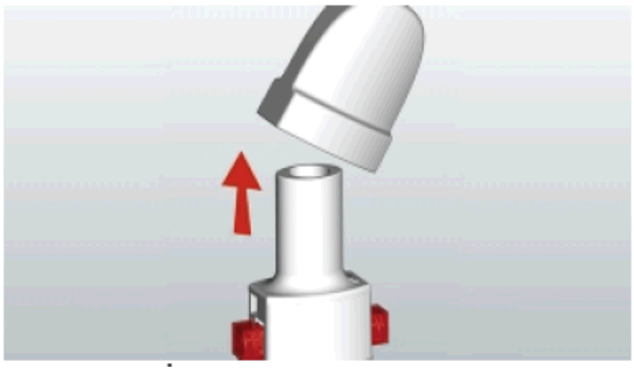
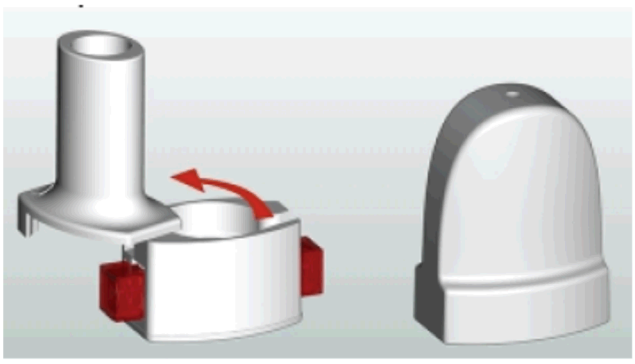
# 18.0 APPENDICES

## 18.1 Appendix 1. Plastiape DPI Inhaler Device - Instructions for Use

**1.** Remove the protective cap from the Plastiape inhaler.

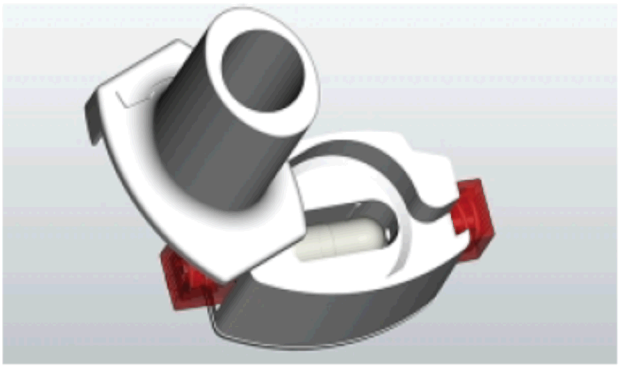


**2.** Open mouthpiece to access the capsule housing.



**3.** Peel back foil from the blister strip and remove capsule from the blister.

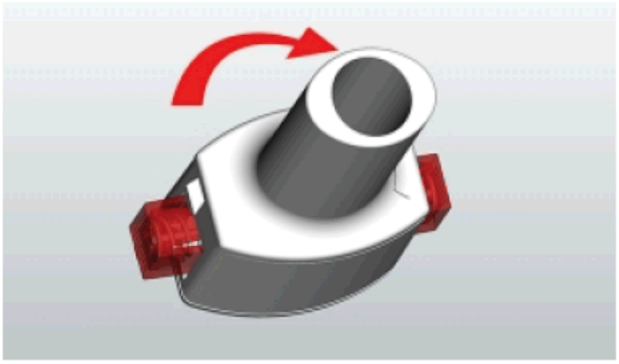
**4.** Load capsule into housing and then shut the mouthpiece.



**5. Pierce the capsule:**

• Hold the inhaler upright with the mouthpiece pointing up.

• Pierce the capsule by firmly pressing together both side buttons at the same time. Do this only once.

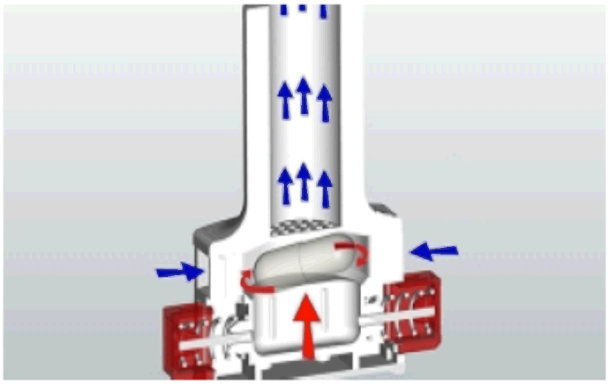


• You should hear a “click” as the capsule is being pierced.

**6. Breathe out:**

Before placing the mouthpiece in your mouth, breathe out fully and do not blow into the mouthpiece.

**7. Inhalation**



To breathe the medicine deeply into your airways:

• hold the inhaler so the side buttons are facing left and right, and do not press the side buttons.

• place the mouthpiece in your mouth and close your lips firmly around it.

• breathe in rapidly but steadily and as deeply as they can.

**8. Note:**

As you breathe in through the inhaler, the capsule spins around in the chamber and you should hear a whirring noise.

**9. Breath hold:**

After you have inhaled the medicine:

• Hold your breath for at least 5-10 seconds or as long as you comfortably can.

• Then breathe out. Open the inhaler to see if any powder is left in the capsule.

**If there is powder left in the capsule:**

• Close the inhaler.

• Repeat steps **6 to 9 (second inhalation)**

**If there is powder left in the capsule:**

• Close the inhaler.

• Repeat steps **6 to 9 (third inhalation)**

Most people are able to empty the capsule with one or two inhalations, but a **maximum** of 3 inhalations can be performed. Please note that 2 capsules are used per dose so steps 3-10 are repeated with the second capsule.

Please ensure you return all unused medication to your study staff at each visit, including all blister packs.

Please ensure you contact study staff if you have further questions. You will receive training prior to your first drug administration by a member off your clinical team. Please ask any questions to your study throughout the study, as required.

## 18.2 Appendix 2. Biomarker Panel

Biomarkers have the potential to impact all aspects of the clinical care of IPF patients including diagnosis and prognosis. The identification of serum biomarkers that are diagnostic for IPF would be helpful for both clinicians and patients, particularly in cases where a surgical lung biopsy had not been obtained or access to dedicated interstitial lung disease/IPF physicians is limited. Secondly, the discovery of peripheral blood biomarkers that reflect disease activity would allow for serial monitoring as well as an objective marker to assess treatment efficacy. Lastly, a biomarker that provides prognostic information about disease course and/or mortality would be valuable for both clinical care and future research study design.

In the context of Galactic-1 study a number of serum biomarkers will be explored:

These may include but are not limited to YKL-40, PAI-1, PDGF-BB, MCP-1, CCL-18, KL-6, CA-125, CA-19, Gal-3 and collagen neoepitopes. Testing will be performed at time points indicated in the Time and Events Table.

**Galectin - 3**

Galectins are a group of soluble β-galactoside-binding lectins that play many important regulatory roles in inflammation, immunologic response and cancer. A total of 15 galectins have been identified. Galectin-3 is the most widely studied member of the galectin protein family [1, 2].

Galectin-3 is a mid-size protein (29 to 35 kDa) consisting of an N-terminal domain with tandem repeats of short amino acid segments (a total of approximately 120 amino acids) linked to a single C-terminal carbohydrate-recognition domain (CRD) of about 130 amino acids. It can interact with carbohydrates, which involves the C-terminal domain, and with unglycosylated molecules, such as cell surface and extracellular receptors, which involves the N-terminal domain [3].

As other galectins, galectin-3 does not contain a signal sequence, therefore it is localized primarily in the cytoplasm, and occasionally, in the nucleus and mitochondria. Galectin-3 is found in epithelial cells, fibroblasts, dendritic cells and inflammatory cells. In addition, galectin-3 can be

secreted and function in extracellular space. It can form pentamers upon binding to multivalent carbohydrates, therefore it is capable of crosslinking glycans on the cell surface, and in this manner initiating transmembrane signaling events and affecting various cellular functions [4].

Galectin-3 is known for its role in tumorigenesis and progression through regulating cell proliferation, apoptosis, cell adhesion, invasion, angiogenesis and metastasis. Expression of galectin-3 is modulated in many different cancers. Measurement of serum galectin-3 can be helpful in diagnosis and prognosis for specific cancer types, such as thyroid and prostate [5].

One of the more interesting and well characterized effects is the role of galectin-3 in the promotion of fibrosis. Fibrogenesis or scarring is a consequence of certain types of injury and inflammation, which are central pathophysiological mechanisms in the development and progression to heart failure. Expression of galectin-3 is low in a healthy human heart; however, as heart failure progresses galectin-3 becomes significantly up-regulated. It is released by activated cardiac macrophages stimulating additional macrophages, pericytes, myofibroblasts, and fibroblasts, which in response signal cellular proliferation and secretion of procollagen I. Procollagen I irreversibly crosslinks to form collagen and results in cardiac fibrosis [6 -10].

Involvement of galectin-3 in fibrosis has also been demonstrated in liver [11] and kidney [12].

Inhibition of galectin-3 appears to prevent progression of fibrosis. Recent publications describe the tetrapeptide, N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP) that causes inhibition of cardiac fibroblast proliferation and collagen synthesis. Ac-SDKP is a naturally occurring anti-inflammatory and antifibrotic peptide that is hydrolyzed almost exclusively by angiotensin-converting enzyme (ACE), and plasma concentration of Ac-SDKP is increased substantially by ACE inhibitors. Rats overexpressing cardiac ACE have decreased Ac-SDKP concentration and increased fibrosis in heart tissue [13]. Other studies include galectin-3 knock-out mice, use of small interfering RNA that can silence galectin-3 gene activity and use of carbohydrate molecules, which can deactivate galectin-3.

Because of the unambiguous association of galectin-3 with the disease development, progression and poor outcome, measurement of galectin-3 in patients diagnosed with IPF, pulmonary hypertension, acute and chronic heart failure may have diagnostic and therapeutic implications.

Recently, the FDA has approved for market an assay manufactured by BG Medicine, Inc. (Waltham, MA) for galectin-3 to supplement standard risk assessment in patients with chronic heart failure [14]. BGM Galectin-3 is currently available at Pacific Biomarkers. The test is based on the common ELISA utilizing two monoclonal antibodies against galectin-3. One rat monoclonal anti-mouse galectin-3 antibody is coated onto the surface of wells as a capture antibody to bind galectin-3 molecules in samples, while the other mouse monoclonal anti-human galectin-3 antibody is provided in solution and functions as the tracer antibody for detecting galectin-3 molecules bound to the capture antibody [15].

Galectin-3 results should be interpreted with caution. Levels may be increased in patients with certain forms of cancer, in other conditions associated with organ fibrosis, and in patients with a history of therapeutic use of murine monoclonal antibodies (IgG) or fragments, or who have known autoimmune disorders. Additionally, specimens with high levels of gamma globulins (>2.5 g/dL) may cause false elevation in results.

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**YKL-40**

Several studies have demonstrated elevated levels of YKL-40, human chitinase-like glycoprotein, in the serum and BALF of IPF patients, with a significant correlation between its serum levels and clinical parameters, including PaO2, DLCO, and serum concentrations of KL-6. Additionally, enhanced expression of YKL-40 protein was found in bronchiolar epithelial cells and alveolar macrophages adjacent to fibrotic lesions by immuno-histochemistry [1-4]. Although the detailed biological function of YKL-40 has not been fully elucidated, recent studies have shown that this glycoprotein has an important role in tissue remodelling processes leading to fibrosis. YKL-40 potently promotes the growth of fibroblasts, endothelial cells, synovial cells, and chondrocytes [5-7].

In the lung, a recent study showed elevated serum YKL- 40 levels in patients with severe asthma, and its levels correlated with thickening of the subepithelial basement membrane and pulmonary function [5, 6]. Taken together, these findings suggest that, besides etiology, YKL-40 can be increased under pathological conditions leading to chronic inflammation and tissue remodelling in the lung. Collectively, these data suggest that increased production of YKL-40 in IPF lungs contributes to tissue remodelling and fibrosis, possibly through its fibrogenic capacity [8-18].

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**KL-6/mucin 1 (MUC-1)**

KL-6/mucin 1 (MUC-1) is a circulating glycoprotein belonging to the MUC-1 class and is expressed on alveolar epithelial cells and bronchiolar epithelial cells. KL-6 exerts antifibrotic and antiapoptotic effects on lung fibroblasts [1]. KL-6 is probably the most extensively studied serum biomarker in ILD, at least in Japan, where it has been used to assess patients in the clinical routine [2]. Serum KL-6 shows good correlation with disease severity, although it does not discriminate between different ILD patterns. Serum levels of KL-6 are significantly elevated in IPF and are associated with increased mortality. A serum cut-off value of ⩾1000 U·mL−1 has been associated with poor prognosis [3]. The presence of the MUC1 568 adenosine to guanine polymorphism (rs4072037) has been found to influence serum KL-6 levels in Caucasian and Japanese subjects, and may need to be considered in the calculation of normal upper limits and cut-off values [4,5].

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**PAI-1**

Plasmin is a key protease involved in the repair of the damaged alveolar epithelium and the plasminogen activator inhibitor-1 (PAI-1) is the major inhibitor of plasminogen activators in plasma and the alveolar space. PAI-1 is one of the most important target genes in the TGF-β/Smad signaling pathway, which can hinder the degradation of ECM composition and promote cell invasion and migration. Multiple reports using preclinical models suggest that PAI-1 deficiency or inhibition of PAI-1 activity attenuates fibrosis. [1]. Mice overexpressing PAI-1 show increased bleomycin-induced lung fibrosis whilst mice deficient in PAI-1 show reduced fibrosis in this model [2,3]. PAI-1 has been shown to be elevated in the BALf in IPF patients compared to control [4,5].

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**CCL18**

CCL18 is a CC chemokine produced mainly by antigen-presenting cells including alveolar macrophages, and is elevated in BALf and serum in patients with IPF [1,2]. CCL18 can stimulate pulmonary fibroblasts and increase collagen production in vitro [3]. In GB-HV-01 10 mg GB0139 treatment trended to reduce serum CCL-18 levels compared to the placebo group.

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**MCP-1**

CC chemokines such as MCP-1 play important roles in the pathogenesis of interstitial lung diseases. Elevated CC chemokine levels have been observed in BALf of patients with IPF (reviewed in [1]). Elevated levels of MCP-1 in BALf may be predictive of a poor outcome in patients with IPF [2]. A deficiency in MCP-1 has been shown to protect mice from bleomycin-induced lung fibrosis [2]. In the GB-HV-01 patient cohort there was a dose dependent trend for a reduction in plasma MCP-1 with GB0139.

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As well as the biomarkers described above there are several biomarkers of note which have shown to be elevated in IPF compared to control and have suggested prognostic significance for disease progression. These include the Nordic collagen neo-epitopes (Jenkins et al., 2015, Lancet. Respir Med. 3(6):462472) as well as epithelial markers SPD, SPA, KL-6, CA-125, CA-19) and matrix

remodeling markers MMP7 and MMP1 (reviewed in Guiot et al., Lung. 2017 Jun;195(3):273-280; Maher et al., 2017, Lancet Respir Med. (12):946-955). In addition, we would like to incorporate the flexibility to measure new analytes as evidence for new biomarkers may evolve during the course of the study.

## 18.3 Appendix 3. Definition of Acute Exacerbations in IPF

Acute respiratory worsening occurs in a small minority of patients with IPF annually (approximately 5–10%) [1-3]. These episodes may occur secondary to common conditions such as pneumonia, pulmonary embolism, pneumothorax, or cardiac failure [4]. When a cause cannot be identified for the acute respiratory decline, the term acute exacerbation of IPF has been used [3, 5-15]. It is presently unclear if acute exacerbation of IPF is simply a manifestation of an unidentified respiratory complication (such as pulmonary emboli, infection) contributing to an acute worsening in a patient with IPF or represents an inherent acceleration in the pathobiological processes involved in IPF.

Regarding the definition of AE in IPF, a revised "conceptual framework" was proposed by an international working group in 2016 [16].

The 2007 proposed definition of an "acute exacerbation" (AE) of IPF included all of the following:

- A previous or concurrent diagnosis of IPF
- Deterioration within 30 days
- New bilateral ground glass opacities and/or consolidation on a background of reticular or honeycomb pattern consistent with usual interstitial pneumonia (UIP)
- No evidence of pulmonary infection by endotracheal aspiration or bronchoalveolar lavage
- Exclusion of alternative causes including left heart failure, pulmonary embolism, or an identifiable cause of acute lung injury

The 2016 revised criteria more accurately reflect today's knowledge of AE-IPF and should allow for better insights into the etiology, treatment, and outcomes of this process [17]. Similar to the definition in 2007, this newly proposed framework defines an AE as "*an acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar*

*abnormality*," but does not set an exact 30 day limit for symptom onset and does not require exclusion of infection. The following diagnostic criteria are proposed:

- A known diagnosis of IPF (diagnosis may be made at the time of acute respiratory deterioration)
- Acute worsening, "typically less than one month's duration"
- Computed tomography of the chest with new bilateral ground glass opacification and/or consolidation superimposed on a background of findings consistent with usual interstitial pneumonia (bibasilar reticular opacities associated with honeycomb changes and traction bronchiectasis)
- Heart failure or fluid overload does not fully explain the worsening.

Based on our understanding that these events may be triggered similar to acute lung injury in the non-IPF patient population, events are further classified into "triggered" (ie, postprocedure, drug toxicity, infection, aspiration) versus "idiopathic" (ie, no inciting event identified). This new classification will allow for a more complete picture of these patients.

**Pathophysiology and risk factors** - While our current understanding of the pathophysiology of AE-IPF is limited, AE has clinical similarities to acute respiratory distress syndrome (ARDS). Both have increased oxygen needs, bilateral ground glass opacities and/or consolidation on imaging, and histopathology demonstrating diffuse alveolar damage [19-22]. It is known that there are multiple causes for ARDS and it is likely the same for those with AE-IPF. Further, IPF patients likely have maladaptive responses to lung injury, demonstrated by altered responses of IPF versus control fibroblasts to stimuli in vitro [23, 24].

There are multiple examples of lung injury that subsequently develop into an AE-IPF [25-28].

- **Microaspiration of gastric contents** – Microaspiration of gastric contents is a proposed risk factor for exacerbations and progression of IPF, based on a meta-analysis of clinical trials that demonstrated patients who received treatment for

gastric reflux had slower decline of forced vital capacity (FVC), although there was no difference in mortality [29].

- **Surgery and thoracic procedures** – Thoracic procedures, such as surgical lung biopsy, lung cancer resection, and bronchoscopy, have been associated with the development of IPF exacerbations [30-34]. Nonthoracic surgical procedures have also been implicated in development of exacerbations [33]. Potential mechanisms include administration of high concentrations of oxygen and volutrauma or barotrauma during mechanical ventilation. However, a causal relationship between IPF exacerbations and procedures is difficult to ascertain due to the retrospective analysis of the studies.
- **Advanced lung disease** – Clinical factors of physiologically advanced IPF are associated with increased rates of AE, including: lower FVC, diffusing capacity of the lung for carbon monoxide (DLCO), and six-minute walk distance [27, 35, 36].
- **Other** – A number of other potential contributors have been implicated, such as evidence of pulmonary hypertension, higher body mass index, coronary artery disease, and treatment with immunosuppressive therapy [36-38].

**Clinical manifestations** - In patients with IPF, an acute exacerbation typically presents with shortness of breath or worsening exercise tolerance that develop over days to weeks, but generally less than one month [17,39]. In a small series of 11 patients, the time from onset of symptoms to hospital admission averaged approximately 13 days [18]. Cough (with or without sputum production) is common; fever and flu-like symptoms may also be present.

On physical examination, the patient may be tachypneic and will typically have bibasilar crackles consistent with the underlying diagnosis of IPF.

Patients typically demonstrate impaired gas exchange, as evidenced by an arterial oxygen tension to fraction of inspired oxygen ratio ($PaO_2/FiO_2$) of less than 225 mmHg or a decrease in the $PaO_2$ of 10 mmHg or more from baseline.

High resolution computed tomography (HRCT) reveals bilateral ground glass or consolidative opacities superimposed on a background of typical HRCT features of IPF (eg, bibasilar reticular opacities, honeycomb changes, traction bronchiectasis).

**Diagnosis** - The diagnosis of AE-IPF is generally made in a patient with known or concurrently diagnosed IPF and the following features [17]:

- An acute, clinically significant respiratory deterioration typically <1 month in duration
- High resolution computed tomography (HRCT) demonstrating new bilateral ground glass opacification and/or consolidation superimposed on a background of findings consistent with usual interstitial pneumonia
- Exclusion of heart failure and fluid overload as significant contributors to the deterioration

Flexible bronchoscopy with bronchoalveolar lavage (BAL) is used to identify infectious agents and exclude malignancy. While the 2007 criteria for AE-IPF required the exclusion of infection, the 2016 criteria do not exclude potential triggers, such as infection, lung procedures/operations, drug toxicity, and aspiration [16, 17]. These potential triggers should be noted, but do not exclude AE-IPF.

**DIFFERENTIAL DIAGNOSIS** — The differential diagnosis of AE-IPF includes venous thromboembolism, infection, and heart failure. A pneumothorax can complicate IPF, but would usually be recognized on a conventional chest radiograph. Pulmonary hypertension developing as a consequence of IPF is also in the differential diagnosis of worsening dyspnea, but would not have the new radiographic opacities associated with AE-IPF.

- **Venous thromboembolism** – IPF is associated with a significantly increased risk of venous thromboembolism (VTE) [40-42]. The suspicion for VTE is increased in patients with obesity, immobilization, malignancy, and prior or family history of VTE.
- **Infection** – For patients who can tolerate the procedure, our standard practice is to perform a full investigation for potential lung infection and to initiate empiric antibiotics for pneumonia while studies are pending, as described. The choice of antibiotics for community-acquired pneumonia is described separately.
- **Heart failure** – Given the average age of individuals with IPF, careful cardiac assessment for heart failure or myocardial infarction is appropriate. We typically begin with serial troponin, brain natriuretic peptide (BNP), and an electrocardiogram. An echocardiogram is not typically a first line assessment, but may be useful to evaluate for heart failure in a subset of patients, such as those with extrathoracic clinical features of heart failure or an elevated BNP.
- **Pulmonary hypertension** – Pulmonary hypertension (group 3), a well-known complication of IPF, also presents with worsening dyspnea, but without increased radiographic opacities. The diagnosis is often suspected in patients with worsening gas transfer without evidence of worsening interstitial lung disease. Plasma BNP is often increased, and Doppler echocardiography can provide an estimate of pulmonary artery systolic pressure. A firm diagnosis requires right heart catheterization.

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## 19.0 A. RESPONSIBILITIES OF THE INVESTIGATOR

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572 – A).

By signing the Form FDA 1572, the investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (non routine/non standard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56 (for IND only), ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50 (only for IND), ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with

the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.

9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.