A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of BG00011 in Patients With Idiopathic Pulmonary Fibrosis

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The primary objective of the study is To evaluate the efficacy of BG00011 compared with placebo in subjects with IPF.The secondary objectives of the study are:* To evaluate the efficacy of BG00011 compared with placebo in subjects with IPF as...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON46196

Source
ToetsingOnline

Brief title
SPIRIT

Condition

- Other condition

Synonym
Idiopathic lung fibrosis, Idiopathic pulmonary fibrosis

Health condition

Idiopathic pulmonary fibrosis

Research involving

Human

Sponsors and support

Primary sponsor: Biogen Idec Research Limited
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: BG00011, efficacy, idiopathic pulmonary fibrosis, safety

Outcome measures

Primary outcome

The primary efficacy endpoint is the Yearly rate of change in FVC (expressed in

mL over 52 weeks) in subjects randomized to BG00011 compared with placebo.

Secondary outcome

The secondary efficacy endpoints are:

* Yearly rate of change in FVC, expressed in percent predicted, over 52 weeks.

* Time to progression, as defined by a composite endpoint, including any of the

following events:

* Absolute decline of 10% predicted in FVC (FVC percent predictedbaseline * FVC

percent predictedprogression *10%).

* Nonelective hospitalization for respiratory events.

* Lung transplantation or death.

* Time to first acute exacerbation, measured in days.

* Proportion of subjects with at least 1 acute exacerbation during the 52 weeks

on study.

* Number of exacerbations during 52 weeks.

* Number of subjects with absolute decline of 10% predicted in FVC (FVC percent

predictedbaseline * FVC percent predictedprogression *10%) over 52 weeks.

* Time to death or lung transplantation, measured in days.

* Time to all nonelective hospitalizations and to nonelective respiratory hospitalizations, measured in days.

* Change in absolute and percent predicted FVC from baseline over time.

* Carbon monoxide diffusion capacity (DLCO) absolute and percent predicted changes from baseline over time.

* Total lung capacity, as measured by plethysmography, absolute and percent predicted changes from baseline over time.

* Change from baseline in 6MWT parameters at Weeks 26 and 52.

* The incidence, severity, outcome, and relationship to study treatment of adverse events and serious adverse events.

* Change from baseline in clinical laboratory test results, vital signs, electrocardiogram (ECG), PFT, and high-resolution computed tomography (HRCT) findings.

* Immunogenicity (antibodies to BG00011).

* Measurement of BG00011 serum concentrations using sparse pharmacokinetic (PK) sample collection at select timepoints during the study.

Other Exploratory endpoints will be defined in detail in the protocol

Study description

Background summary

IPF is a serious, chronic, progressively fatal lung disease involving replacement of normal lung tissue with fibrotic scar tissue. IPF is a rare disease that predominantly affects the middle aged and elderly (after age 60 years; median age at diagnosis: 66 years). Patients with IPF typically live for only 3 to 5 years after diagnosis, with a median survival time of approximately 3.5 years from diagnosis. IPF significantly impairs health related quality of life, and the majority of patients also have serious comorbid conditions. Clinical features of IPF include progressive cough, dyspnea, restrictive ventilatory defect, and progressive fibrosis and destruction of the lung parenchyma. The diagnosis is made in patients with the appropriate clinical features and the histologic pattern of usual interstitial pneumonia (UIP) [based on lung biopsy or high-resolution computed tomography (HRCT)]. Challenging factors for clinical management include older age, comorbid conditions, and acute unpredictable exacerbations. Acute exacerbations of IPF are defined as sudden (typically less than 30 days onset) unexplained worsening of underlying disease, including new radiological infiltrates (based on HRCT) or UIP pattern. The progressive deterioration of lung function results in respiratory failure. The prognosis following acute exacerbation and deterioration of lung function is poor, with 1-year and 5-year survival rates of 56.2% and 18.4% following acute exacerbation, which is considerably shorter than in IPF patients without acute exacerbation.
The underlying pathophysiology of IPF is unknown. Whatever the inciting event is, it triggers a TGF-* mediated fibrogenic response. As a part of this response, alveolar epithelial cells via the production of signaling mediators, including TGF-*, tumor necrosis factor, endothelin 1, and cytokines, induce proliferation and activation of fibroblasts and myofibroblasts. This leads to secretion of connective tissue matrix molecules, such as collagen, to replace the damaged tissue but also displaces healthy tissue leading to scarring and ultimately organ failure .
To date, no therapies have demonstrated efficacy in halting IPF disease progression. Historically, disease-modifying agents for IPF have included nonspecific anti-inflammatory or immunosuppressive agents (i.e., corticosteroids, azathioprine, and cyclophosphamide), which were used in the United States despite the absence of clinical studies to demonstrate their efficacy, with some ultimately demonstrating harm.
Two recently approved therapies, pirfenidone (Esbriet®) and nintedanib (Ofev®), have demonstrated a similar ability to slow deterioration in lung function by nearly 50%; however, patients are still faced with death or lung transplantation as the ultimate outcome.

Therapies that can halt or reverse disease progression, increase life expectancy, and improve quality of life while demonstrating minimal side effects remain a treatment goal for patients diagnosed with IPF.

BG00011 (humanized, immunoglobulin G subtype 1 [IgG1] anti-alpha v beta 6 [*v*6] monoclonal antibody [mAb]), formerly known as STX-100, is being developed by Biogen as a novel therapeutic treatment for patients with

idiopathic pulmonary fibrosis (IPF). BG00011 binds to the *v*6 integrin, which inhibits the integrin from binding to and activating the latent form of transforming growth factor-beta (TGF *). TGF-* plays a critical role in the initiation and maintenance of fibrosis, and targeted inhibition of the *v*6/ TGF-* pathway may prevent the development of fibrosis, organ scarring, and organ failure. The clinical development plan for BG00011 is designed to demonstrate that blocking *v*6 and inhibiting the activation of TGF-* in patients with IPF can prevent or reduce the progression of fibrosis, resulting in preservation of pulmonary function.

Study objective

The primary objective of the study is To evaluate the efficacy of BG00011 compared with placebo in subjects with IPF.
The secondary objectives of the study are:
* To evaluate the efficacy of BG00011 compared with placebo in subjects with IPF as determined by change in percent predicted FVC.
* To assess progression-free survival in subjects who receive BG00011 compared with placebo.
* To assess the occurrence of IPF exacerbation (using modified diagnostic criteria for acute IPF exacerbation derived from [Collard 2007]) in subjects who receive BG00011 compared with placebo.
* To assess the incidence of absolute decline in FVC *10% in subjects who receive BG00011 compared with placebo.
* To assess the time to death or lung transplantation in subjects who receive BG00011 compared with placebo, and the transplant-free survival rate at Week 26 and Week 52.
* To assess the time to nonelective hospitalizations in subjects who receive BG00011 compared with placebo.
* To assess additional pulmonary function test (PFT) findings in subjects who receive BG00011 compared with placebo.
* To assess performance on the 6 Minute Walk Test (6MWT) in subjects who receive BG00011 compared with placebo.
* To evaluate the safety and tolerability of BG00011.
* To evaluate the serum concentration of BG00011

Study design

Phase 2b randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, PK, and tolerability of BG00011 in subjects with IPF.
Subjects will be stratified by background therapy status (subjects receiving background therapy and subjects not receiving background therapy) and randomized in a 1:1 ratio of BG00011 to placebo. Enrollment will also be monitored to ensure that subjects receiving background therapy represent approximately 50% of each treatment group.

Subjects will receive weekly injections of BG00011 or placebo, as a solution for SC injection in a prefilled syringe, for 52 consecutive weeks (a total of 52 doses). The first dose will be administered at the Baseline (Day 0) Visit. The rest of the doses may be administered independently (e.g., not at the study site) by the subject or the subject*s caregiver.
Background therapy for IPF with pirfenidone or nintedanib will be allowed during the study.
An independent data safety monitoring board (DSMB) will review the unblinded safety and available PK data throughout the study (at least quarterly) to assess the overall safety profile.

Study duration for an individual subject is approximately 65 weeks, including a Screening Visit up to 5 weeks prior to the first dose of study treatment, a Placebo-Controlled Treatment Period of 52 weeks, and a Safety Follow-Up Visit 8 weeks after the end of the Treatment Period.

Intervention

Patients should visit the clinics and be willing to receive their study drug or placebo according to the dosing schema.

Furthermore their data of Medical history and demographic data will be collected. They must undergo physicial and vital signs examinations. An electrocardiogram, spirometry plethysmography 6-minute walk test and carbon monoxide diffusion capacity test will be made. Blood and urine will be collected. Several Questionnaires need to be filled in at different timepoints. They will be tested for HIV, HCV and pregnancy if applicable.

Study burden and risks

As a first-in-class treatment for patients with IPF, the reduction in pSMAD2 levels and gene expression required for clinical efficacy is unknown. Across multiple mouse models of lung fibrosis, *v*6-blocking antibody treatment with dosing between 0.3 and 1.0 mg/kg leads to significant reductions in pSMAD2 and reduced collagen expression (a marker of fibrosis) without inducing lung inflammation. The steep dose response in pSMAD2 is consistently observed in subjects with IPF (Study 203PF201), in nonhuman primate biomarker studies, and in the rodent models of epithelial injury and fibrotic diseases.

As of 28 February 2017, a total of 61 subjects (31 subjects with IPF and 30 healthy volunteers) have received BG00011 in 2 completed clinical studies, Phase 1 Study STX-001 and Phase 2a Study 203PF201.
STX-001, BG00011 was well tolerated, with no deaths, serious adverse events (SAEs), or premature discontinuations related to an AE. No clinically significant changes were noted for any safety measures including AEs, physical examination, vital signs, or clinical laboratory parameters, including

pulmonary function tests (PFTs). AEs occurred in 21 of 30 subjects (70%) who received BG00011 and 8 of 10 subjects (80%) who received placebo. The most common AEs were headache, diarrhea, vomiting, arthropod stings, nasopharyngitis, and nasal congestion.
Study 203PF201 multiple SC doses of BG00011 up to 1.0 mg/kg were generally well tolerated in the population of subjects with IPF, with the incidence and severity of AEs, and changes in physical examination, vital signs, or clinical laboratory parameters comparable to those expected in the IPF population.
Based on a detailed review of the safety, PK, and PD data for Study 203PF201, Biogen considers that the potential benefit/risk of BG00011 is acceptable for dosing in subjects with IPF at doses not exceeding 1.0 mg/kg.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Female subjects must be surgically sterile, postmenopausal (minimum 1 year without menses), or agree to use 1 or more forms of highly effective contraception from the time of signing of the informed consent form (ICF) until 3 months after the last injection of study medication. Male subjects must also agree to use 1 or more forms of highly effective contraception for either themselves or heir partners from signing of ICF until 4 months after last injection of study medication.
- Diagnosed with Idiopathic pulmonary fibrosis (IPF).
- Combination of high-resolution computed tomography (HRCT) pattern and, if one has been obtained, surgical lung biopsy pattern, consistent with diagnosis of IPF.
- Carbon monoxide diffusion capacity (DLco) (corrected for hemoglobin): 30% to 79% predicted of normal at Screening, with no clinically significant deterioration between the Screening Visit and randomization, as determined by the Investigator.
- Forced (expiratory) vital capacity (FVC) *50% predicted of normal at Screening, with no clinically significant deterioration between the Screening Visit and randomization, as determined by the Investigator.
- If a subject is taking nintedanib or pirfenidone, they must be on a stable dose for at least 8 weeks prior to randomization. ;for more inclusion criteria please see the protocol

Exclusion criteria

- Unable to perform pulmonary functional tests (PFTs) or undergo HRCT procedure.
- Peripheral capillary oxygen saturation (SpO2) <90% at rest (if on oxygen supplementation, must be *2 L/min at rest).
- Airway obstruction (i.e., prebronchodilator FEV1/FVC <0.7) or evidence of a bronchodilator response as defined by an absolute increase of *12% and an increase of *200 milliliters (mL) in FEV1 or FVC, or both, after bronchodilator use, compared with the values before bronchodilator use at Screening.
- End-stage fibrotic disease likely requiring organ transplantation within 12 months, or if the subject has initiated active evaluation for organ transplantation.
- The extent of emphysema in the lungs exceeds fibrosis, based on central review of HRCT scans.
- Body weight <60 kg at Screening.
- History of or ongoing malignant disease, including solid tumors and hematologic malignancies, with the exception of basal cell carcinomas, squamous cell carcinomas, and carcinoma in situ of the cervix that have been completely excised and considered cured >2 years prior to Screening.
- Significant cardiac disease (e.g., New York Heart Association Class 3 or 4; myocardial infarction within the past 6 months; unstable angina; coronary angioplasty or coronary artery bypass graft within the past 6 months; uncontrolled atrial or ventricular cardiac arrhythmias; or pulmonary hypertension requiring pharmacologic treatment).
- Clinical diagnosis of any connective tissue disease (including but not limited to scleroderma, polymyositis/dermatomyositis, systemic lupus erythematosus, and rheumatoid arthritis) or a

diagnosis of interstitial pneumonia with autoimmune features as determined by the Investigator.
- Other disease that may interfere with testing procedures or, in the judgment of the Investigator, may interfere with study participation or may put the patient at risk when participating in this study.
- Other unspecified reasons that, in the opinion of the Investigator or Biogen, make the subject unsuitable for enrollment.
for more exclusion criteria please see the protocol

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-10-2018
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BG00011
Generic name:	n/a

Ethics review

Approved WMO Date:	24-05-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-10-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-03-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-03-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-003158-18-NL
CCMO	NL65809.056.18