A Phase IIb, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Astegolimab in Patients with Chronic Obstructive Pulmonary Disease

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This study has been transitioned to CTIS with ID 2023-507093-40-00 check the CTIS register for the current data. EFFICACY OBJECTIVESThe primary efficacy objective for this study is to evaluate the efficacy of astegolimab compared with placebo The...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Bronchial disorders (excl neoplasms)
Study type	Interventional

Summary

ID

NL-OMON54477

Source
ToetsingOnline

Brief title
GB43311

Condition

- Bronchial disorders (excl neoplasms)

Synonym
Chronic Obstructive Pulmonary Disease (COPD)

Research involving
Human

Sponsors and support

Primary sponsor: Genentech, Inc. c/o F. Hoffmann-La Roche Ltd
Source(s) of monetary or material Support: Genentech;Inc

Intervention

Keyword: Chronic Obstructive Pulmonary Disease, COPD, exacerbations

Outcome measures

Primary outcome

Efficacy

-Annualized rate of moderate and severeCOPDexacerbations over the 52-week

treatment period

A moderate COPD exacerbation is defined as new or increased COPD symptoms

(e.g.,dyspnea, sputum volume, and sputum purulence) that lead to treatment

(duration >=3 days) with systemic corticosteroids (oral, IV, or intramuscular

[IM]) at a dose of >10 mg/day prednisolone equivalent and/or antibiotics.

A severe COPD exacerbation is defined as new or increased COPD symptoms that

lead to hospitalization (duration >= 24 hours) or lead to death.

Secondary outcome

Efficacy

• Time to first moderate or severe COPD exacerbation during the 52-week

treatment period

• Absolute change from baseline in health-related quality of life (HRQoL) at

Week 52, as assessed through the St. George*s Respiratory Questionnaire-COPD

(SGRQ-C) total score

• Proportion of patients with improvement in HRQoL, defined as a decrease from

baseline of * 4 points in SGRQ-C total score, at Week 52

• Absolute change from baseline in post-bronchodilator forced expiratory volume in 1 second (FEV1) (liters) at Week 52

• Absolute change from baseline in Evaluating Respiratory Symptoms in COPD (E-RS:COPD) total score at Week 52

• Annualized rate of severe COPD exacerbations over the 52-week treatment period

• Absolute change from baseline in five-repetition sit-to-stand test (5STS) time (seconds) at Week 52

• Incidence and severity of adverse events

Safety

• Incidence and severity of adverse events, with severity determined according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (HHS 2017) (hereafter referred to as the DAIDS toxicity grading scale), with slight modifications for clarity and for alignment with internal practices

• Change from baseline in targeted vital signs

• Change from baseline in targeted clinical laboratory test results and ECGs

Pharmacokinetic (PK)

• Serum concentration of astegolimab at specified timepoints

Immunogenicity

• Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs

during the study

Study description

Background summary

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death worldwide. COPD is recognized as a progressive, heterogeneous disease. COPD exacerbations represent the largest burden in terms of healthcare utilization, patient morbidity, and risk of mortality.
Therefore, interventions that target the reduction of COPD exacerbations are expected to have the most benefit for patients with COPD. Despite a large unmet need, there are currently limited options for pharmacotherapy specifically targeted at reducing exacerbations.
Despite these treatment options, deceleration of disease progression and prevention of COPD exacerbations are still unmet needs.
Astegolimab (also known as RO7187807 or MSTT1041A) is a fully human, IgG2 monoclonal antibody that binds with high affinity to the IL-33 receptor, ST2, thereby blocking the signaling of interleukin-33 (IL-33), an inflammatory cytokine of the interleukin-1 (IL*1) family and member of the *alarmin* class of molecules.
Astegolimab, an anti-ST2 monoclonal antibody that acts as a pure, competitive antagonist to block IL-33 signaling, is hypothesized to have the potential to treat COPD by reducing exacerbations without inhibiting the development of protective adaptive immunity and viral clearance
Combined, nonclinical and clinical studies have demonstrated that astegolimab has a well-tolerated safety profile and strong rationale supporting its potential benefit in patients with COPD who have frequent exacerbations, supporting further clinical development in this indication.

Study objective

This study has been transitioned to CTIS with ID 2023-507093-40-00 check the CTIS register for the current data.

EFFICACY OBJECTIVES
The primary efficacy objective for this study is to evaluate the efficacy of astegolimab compared with placebo
The secondary efficacy objective for this study is to evaluate the efficacy of astegolimab compared with placebo

SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety of astegolimab compared with placebo

PHARMACOKINETIC OBJECTIVES
The pharmacokinetic (PK) objective for this study is to characterize the astegolimab PK profile

IMMUNOGENICITY OBJECTIVES
The immunogenicity objective for this study is to evaluate the immune response to astegolimab

Study design

This is a Phase IIb, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety and pharmacokinetics of astegolimab in combination with standard of care (SOC) compared with placebo in combination with SOC in patients with COPD who are former or current smokers and have a history of frequent exacerbations.
Following a screening period of at least 7 days to up to 4 weeks, patients will be randomized in a 1:1:1 ratio to one of three treatment arms to receive blinded treatment with either astegolimab or placebo. Randomization will be stratified by smoking status at screening (former smoker vs. current smoker) and region.
The first dose of study drug (astegolimab or placebo) will be administered on Day 1; treatment will continue through at least Week 50, followed by a 12-week safety follow-up period. Patients will return to the clinic every 2 weeks through the treatment completion visit at Week 52 (or the end of an additional treatment period, as described below, if applicable). The primary endpoint analyses will be conducted using the 52-week treatment period data for all patients.
An independent Data Monitoring Committee (iDMC) will monitor patient safety during the study and conduct an interim analysis for futility. Patients who complete the Week 52 visit before the interim analysis will continue to receive blinded treatment beyond the 52 week treatment period for an additional 36 weeks or until the interim analysis results are known, whichever is sooner.
If a separate open-label extension (OLE) study, Study GB43374, is open and available in their respective country, all patients enrolled in this study and who have completed the Week 52 visit will be given the option to either participate in OLE Study GB43374, if eligible, or enter the safety follow-up period. If OLE Study GB43374 is not opened, all patients who complete the Week 52 visit, including those patients receiving continued blinded treatment after Week 52, will enter the safety follow-up period. All patients will undergo a safety follow-up visit 12 weeks after their final dose of study drug (regardless of the length of treatment received).
Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per patient) at the investigator's discretion. The investigator

will record reasons for screen failure in the screening log.

Intervention

Patients randomized to the astegolimab treatment arms will be administered one of the following dosing regimens:
• Astegolimab 476 mg SC every 2 weeks (Q2W)
• Astegolimab 476 mg SC every 4 weeks (Q4W)
To ensure that all study patients undergo the same visit schedule, patients randomized to the Q4W dosing arm will alternate between injections of astegolimab and placebo every 2 weeks (beginning with astegolimab on Day 1), thus receiving astegolimab every 4 weeks.
Each dose of astegolimab will be administered as two SC injections (for a total of 3.4 mL), with each injection administered on a different side of the abdomen (i.e., right or left).
PLACEBO
Patients in the placebo (control) arm will be administered each dose of placebo as two SC injections Q2W, with each injection administered on a different side of the abdomen (i.e., right or left).

Study burden and risks

The medicinal product to be investigated may cause side effects. Side effects can be mild to severe or even life-threatening, and they can vary from person to person.

Astegolimab has been tested in 7 studies with humans, including one study with people with COPD. In clinical studies that have been completed so far, which have included over 690 individuals who received astegolimab, there were no identified risks with taking astegolimab. The potential side effects based on human and laboratory studies or knowledge of new injectable or similar drugs, are listed below. There may be side effects that are not known at this time.
Potential Side Effects
• Reaction near the area where the study drug is injected with symptoms that may include redness, tenderness or pain, bruising, warmth, swelling, itching, and/or infection at the injection site.
• Allergic reaction with symptoms such as fever, chills, low blood pressure, rash, headache, nausea and sometimes vomiting, cramping abdominal pain or incontinence. More severe allergic reactions can cause loss of consciousness, severe skin reactions, difficulty breathing or swallowing, and/or a decrease in blood pressure and could be life threatening.
• Decrease or change in the body*s protective response to infections.
• Laboratory studies in mice and cell cultures on the pathway that astegolimab affects (the IL-33 pathway) suggest a possible risk of worsening of heart diseases where heart disease was already present.
• Risk that the immune system might develop antibodies; this may cause the drug

not to work or could increase the chances of getting an allergic reaction, but it is not known if these antibodies will cause side effects.

The medicinal product can also have side effects that we do not know about at the moment.
There may be some discomfort from the measurements during the study, such as the blooddraws, spirometry and sit-to-stand test, which require effort on behalf of the participant. Participants are exposed to radiation during the chest X-rays.
Taking part in the study will cost extra time and participants are asked to comply with the study agreements

Contacts

Public
Genentech, Inc. c/o F. Hoffmann-La Roche Ltd

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Basel 4070
CH
Scientific
Genentech, Inc. c/o F. Hoffmann-La Roche Ltd

Grenzacherstrasse 124 1
Basel 4070
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

•Signed Informed Consent Form •Age 40-90 years at time of signing Informed Consent Form •Ability to comply with the study protocol •Documented physician diagnosis of COPD made at least 12 months prior to screening •History of frequent exacerbations, defined as having had two or more moderate or severe exacerbations occurring within a 12-month period in the 24 months prior to screening. Exacerbations should have been treated with systemic corticosteroids and/or antibiotics. A moderate COPD exacerbation is defined as new or increased COPD symptoms (e.g., dyspnea, sputum volume, and sputum purulence) that lead to treatment (duration => 3 days) with systemic corticosteroids (oral, IV, or IM) at a dose of >10 mg/day prednisolone equivalent and/or antibiotics. Prior use of antibiotics alone does not qualify as a moderate exacerbation, unless the use was specifically for the treatment of worsening symptoms of COPD. A severe COPD exacerbation is defined as new or increased COPD symptoms that lead to hospitalization (duration >24 hours) or lead to or death. •Post-bronchodilator FEV1 =>20 and <80% of predicted normal value at screening, as verified by over-reader •Post-bronchodilator FEV1/FVC < 0.70 at screening, as verified by over-reader •mMRC score => 2 at screening •Current smoker or former smoker with a minimum of 10 pack-year history (e.g., 20 cigarettes/day for 10 years) A former smoker is defined as meeting the criteria above but has not used inhaled tobacco products or inhaled marijuana within 6 months prior to screening, through use of cigarettes, cigars, electronic cigarettes, vaporizing devices, or pipe. Note that at screening, patients who meet the protocol definition of current smoker will receive smoking cessation counseling. •History of one of the following combinations of optimized, stable, standard-of-care COPD maintenance therapy for at least 4 weeks prior to screening, with no anticipated changes in therapy prior to initiation of study drug and throughout the study: Inhaled corticosteroid (ICS) => 500 mcg/day fluticasone propionate dose-equivalent plus long-acting beta-agonist (LABA). - Long-acting muscarinic antagonist (LAMA) plus LABA. - ICS => 500 mcg/day fluticasone propionate dose-equivalent plus LAMA plus LABA •Demonstrated ability to use and comply with electronic diary (eDiary) requirements, defined as completion of all questions on at least 5 out of 7 consecutive days within the 14 days after the screening visit Patients unable to demonstrate compliance with the eDiary within the first 2 weeks of screening will be screen failed. Patients will have the opportunity to demonstrate eDiary compliance if re-screened. •For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below: Women must remain abstinent or use contraceptive methods with a failure rate of <1% per year during the treatment period and for 12 weeks after the final dose of Astegolimab. A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (=> 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g.,

Mu*llerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations. Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form. •For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below: With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 12 weeks after the final dose of Astegolimab to avoid exposing the embryo. Men must refrain from donating sperm during this same period. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence. •For patients enrolling in the Airway Biomarker Substudy(at participating sites): ability to produceat least 1mL of sputum spontaneously or via sputum inductionat screening

Exclusion criteria

Pregnant or breastfeeding, or intending to become pregnant during the study or within 12 weeks after the final dose of study drug. Women of childbearing potential must have a negative serum pregnancy test result at screening and a negative urine pregnancy test on Day 1 prior to initiation of study drug. •Current documented diagnosis of asthma according to the Global Initiative for Asthma guidelines or other accepted guidelines within 5 years prior to screening •History of clinically significant pulmonary disease other than COPD (e.g., pulmonary, fibrosis, sarcoidosis, chronic pulmonary embolism or primary pulmonary hypertension, alpha-1-antitrypsin deficiency) •Clinically significant abnormalities requiring clinical follow-up as indicated by chest X-ray or chest CT scan performed within 6 months prior to screening Chest X-ray must be performed at screening if results from a chest X-ray or chest CT scan performed within 6 months prior to screening are not available. •Presence of risk factors for aspiration pneumonia (e.g., neurologic disease such as uncontrolled epilepsy) in the opinion of the investigator •History of long-term treatment with oxygen at > 4.0 liters/minute. While breathing supplemental oxygen, patient should demonstrate an oxyhemoglobin saturation of => 89%. •History of a severe allergic reaction or anaphylactic reaction to a biologic agent or known hypersensitivity to any component of the study drug •Lung volume reduction

surgery or procedure within 12 months prior to screening •Participation in or planned participation in a new pulmonary rehabilitation program within 4 weeks prior to screening and throughout the study treatment period. Patients who are in the maintenance phase of a rehabilitation program are eligible. •History of lung transplant •Occurrence of protocol-defined moderate or severe COPD exacerbation, COVID-19, upper or lower respiratory infection, pneumonia, or hospitalization of => 24 hours duration within 4 weeks prior to initiation of study drug •Any prior treatment with Astegolimab •Treatment with oral, IV, or IM corticosteroids (>10 mg/day prednisolone equivalent) within 4 weeks prior to initiation of study drug •Treatment with investigational therapy within 3 months or 5 drug-elimination half-lives (whichever is longer) prior to screening •Treatment with a licensed biologic agent (e.g., omalizumab, dupilumab, and/or anti-IL-5 therapies) within 3 months or 5 drug-elimination half-lives (whichever is longer) prior to screening •Initiation of a methylxanthine preparation, maintenance macrolide therapy, and/or PDE4 inhibitor within 4 weeks prior to screening •Initiation of or change in non-biologic immunomodulatory or immunosuppressive therapy within 3 months prior to screening •Treatment that is considered palliative (e.g., for life expectancy <12 months) •Use of any of the following treatments within 4 weeks prior to screening, or any condition that is likely to require such treatment during the course of the study, unless the treatment is deemed acceptable by the investigator, in consultation with the Medical Monitor: - Treatment with immunoglobulin or blood products. - Treatment with any live or attenuated vaccine (including any approved, live SARS-CoV-2 vaccine) within 4 weeks prior to screening or during the screening period, or anticipated need for live, attenuated vaccine during the course of the study, unless the vaccine is deemed medically necessary and no inactivated vaccine alternatives are available. •Administration of non-live SARS-CoV-2 vaccine (with full marketing authorization or temporary), including those delivered by non-replicating viral vectors, within 7 days prior to initiation of study drug •Planned surgical intervention during the study •Positive hepatitis C virus (HCV) antibody test result accompanied by a positive HCV RNA test at screening •Unacceptable test results for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and total hepatitis B core antibody (HBcAb) at screening, defined as meeting either of the following criteria: - Positive HBsAg test at screening. - Negative HBsAg test at screening, with negative HBsAb test accompanied by positive total HBcAb test, followed by quantitative hepatitis B virus (HBV) DNA => 20 IU/mL. Inability to perform HBV DNA test is exclusionary. Patients with a negative HBsAg test and positive HBsAb test are eligible. •Known immunodeficiency including, but not limited to, HIV infection Patients must have a negative HIV test result at screening or within 3 months prior to screening. •Known evidence of active or untreated latent tuberculosis •Substance abuse, as determined by the investigator, within 12 months prior to screening •History of malignancy within 5 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year overall survival rate > 90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, or

ductal carcinoma in situ •Any other serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study •Unstable cardiac disease, myocardial infarction, or New York Heart Association Class III or IV heart failure within 12 months prior to screening •History or presence (as verified by over-reader)of an abnormal ECG that is deemed clinically significant by the investigator, including complete left bundle branchblock or second- or third-degree atrioventricular heart block •QT interval corrected through use ofFridericia*s formula (QTcF)(as verified by over-reader)>450 ms if patient is male or QTcF >470 ms if patient is female For male or female patients with QRS >120: QTcF >480 ms. •History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as structural heart disease (e.g., severe left ventricular systolic dysfunction, significant left ventricular hypertrophywith strain), or family history of sudden unexplained death or long QT syndrome

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:	Recruiting
Start date (anticipated):	21-06-2022
Enrollment:	23
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Astegolimab
Generic name:	Astegolimab

Ethics review

Approved WMO Date:	16-11-2021
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-12-2021
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-06-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-08-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-10-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	31-10-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-03-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-03-2023
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-12-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-01-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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
EU-CTR	CTIS2023-507093-40-00
EudraCT	EUCTR2021-002045-15-NL
ClinicalTrials.gov	NCT05037929
CCMO	NL78612.028.21