A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Dupilumab in Patients with Allergic Bronchopulmonary Aspergillosis

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Ethical review	Approved WMO
Status	Pending
Health condition type	Allergic conditions
Study type	Interventional

Summary

ID

NL-OMON56225

Source
ToetsingOnline

Brief title
LIBERTY-ABPA AIRED (0456/0300)

Condition

- Allergic conditions

Synonym
ABPA, Hinson-Pepys' disease

Research involving
Human

Sponsors and support

Primary sponsor: Regeneron Pharmaceuticals Inc.
Source(s) of monetary or material Support: The study sponsor as indicated in B7.

Intervention

Keyword: Allergic bronchopulmonary aspergillosis, Dupilumab, Phase 2

Outcome measures

Primary outcome

The primary endpoint in the study is change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV1) compared to placebo.

Secondary outcome

The secondary endpoints are:

1. Annualized rate of severe respiratory exacerbations, defined as new onset of symptoms or clinical worsening of respiratory symptoms requiring systemic corticosteroid treatment for >=3 consecutive days; for patients who are on maintenance systemic corticosteroids, at least double the dose of maintenance systemic corticosteroids for >=3 consecutive days (with or without antibiotic therapy if indicated).
2. Annualized rate of ABPA-related exacerbations, defined as severe respiratory exacerbations (as defined above) that are associated with a doubling of serum total IgE from the prior pre-exacerbation value, over the 52 week treatment period compared to placebo
3. Annualized rate of severe respiratory exacerbations requiring either hospitalization or observation for >24 hours in an ED/urgent care facility during the 52 week treatment period compared to placebo

4. Change from baseline in ACQ-5 compared to placebo over the 52-week treatment period

5. Change from baseline in SGRQ total score compared to placebo over the 52 week treatment period

6. Percentage of participants achieving a reduction in the SGRQ score of 4 points or greater from baseline to weeks 12, 24, 36, and 52 compared to placebo

7. Percent change from baseline in total IgE in serum compared to placebo over the 52 week treatment period

8. Percent change from baseline in A fumigatus-specific IgE in serum compared to placebo over the 52-week treatment period

9. Percent and absolute change from baseline in FeNO compared to placebo over the 52 week treatment period

10. Incidence of treatment-emergent adverse events (TEAEs)

11. Immunogenicity of dupilumab, as determined by the incidence, titer, and clinical impact of treatment emergent ADA to dupilumab

12. Concentrations of functional dupilumab in serum by treatment regimen

Study description

Background summary

Allergic bronchopulmonary aspergillosis (ABPA) is a progressive, immunologic lung disease caused by hypersensitivity to the fungus Aspergillus fumigatus (A fumigatus) that occurs in patients with asthma or cystic fibrosis. The prevalence of ABPA is estimated to be 1% to 3% in patients with severe asthma referred for specialty care. Clinically, asthma patients with ABPA have a more severe clinical course with poorly controlled asthma, poor response to treatment, and frequent episodes of exacerbations compared to patients with asthma who do not have ABPA. In addition, ABPA is often associated with thick

mucoid secretions that can lead to obstruction of large and small airways, bronchiectasis (which does not otherwise occur in asthma), and lung function impairment beyond that seen in a typical asthma patient.

The current mainstay of treatment for ABPA is administration of systemic corticosteroids, with many patients becoming corticosteroid-dependent to control the disease. However, not all patients respond to systemic corticosteroids. Long-term use of systemic corticosteroids is not recommended due to the lack of evidence supporting prevention of progressive bronchial destruction and the potential for serious side effects associated with chronic use. ABPA complicating asthma does not respond clinically to conventional asthma therapy including high doses of inhaled corticosteroids (ICS). Various antifungal agents (eg, itraconazole, voriconazole, ketoconazole, amphotericin B) are used as adjunctive treatments for ABPA in patients who respond poorly to corticosteroids in an effort to reduce the fungal antigenic stimulus. However, clinical response to antifungals is variable, antifungal therapy is not curative, and the side effects of antifungals - which include nausea, vomiting, diarrhea, fever, rash, headache, and hepatotoxicity * limit their use. Long-term studies to evaluate the effect of treatment with these agents to modify the progressive decline in lung function in ABPA are lacking.

Thus, there is an unmet need for more effective and safe treatments that target the immunological underpinnings of ABPA to prevent irreversible airway and parenchymal disease, improve clinical symptoms, and obviate the need for systemic corticosteroids with their accompanying safety concerns.

Dupilumab is a human monoclonal IgG4 antibody that inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the type I receptor and both IL-4 and IL-13 signaling through the type II receptor. Blocking IL-4Rα with dupilumab inhibits IL-4 and IL-13, key cytokines that drive the type 2 inflammatory response, including the release of proinflammatory cytokines, chemokines, nitric oxide, and IgE. Dupilumab, therefore, may have the potential to treat ABPA, a disease driven by type 2 inflammation.

This study is designed to provide evidence of the efficacy and safety of dupilumab in patients with ABPA who remain uncontrolled despite ICS.

Study objective

The primary objective of the study is to evaluate the efficacy of dupilumab on the lung function in patients with ABPA.

The secondary objectives of the study are:
• To evaluate the effects of dupilumab on exacerbations in patients with ABPA
• To evaluate the effects of dupilumab on ABPA-related exacerbations

• To evaluate the effects of dupilumab on hospitalization/emergency department (ED)/urgent care visits in patients with ABPA
• To evaluate the effects of dupilumab on asthma control in patients with ABPA
• To evaluate the effects of dupilumab on health-related quality of life (HRQoL) in patients with ABPA
• To evaluate the effects of dupilumab on serum total IgE and Aspergillus-specific IgE concentrations
• To evaluate the effects of dupilumab on FeNO levels
• To evaluate safety and tolerability of dupilumab in patients with ABPA
• To evaluate dupilumab concentrations in serum and the incidence of anti-dupilumab antibodies in patients with ABPA

Study design

Phase 2, global, multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate efficacy and safety of dupilumab in patients with ABPA. The 3 study periods include a screening period, a randomization period and post-treatment follow-up period. Patients will be randomized 1:1 to receive either dupilumab 300 mg given subcutaneously (SC) after a loading dose of 600 mg, or matching placebo given SC every 2 weeks (Q2W).

Intervention

Dupilumab, as 150 mg/mL solution for SC injection. Loading dose of 600 mg on day 1, followed by 300 mg SC, Q2W
Placebo, matching dupilumab formulation without addition of protein. Administered SC, Q2W

Study burden and risks

Please refer to appendix D of the subject information sheet for an overview of the side effects and possible risks of the study.

Contacts

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Regeneron Pharmaceuticals Inc.

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

•Males and females >=12 years of age at screening
Diagnoses of both ABPA and asthma.
•On a maintenance therapy for their asthma with controller medication which must include ICS and may include 1 or more additional controller medications including a LABA, LTRA, and/or LAMA, etc for at least 12 weeks, with a stable dose and regimen with no change in the dose or frequency of administration for at least 4 weeks prior to the screening visit, and between the screening and baseline/randomization visits
•For patients on OCS: must be on a chronic stable dose (no change in the dose) of OCS of up to 10 mg/day (for patients taking daily corticosteroids) or 30 mg every alternate day (for patients taking alternate day corticosteroids) of OCS (prednisone/prednisolone or the equivalent) for at least 4 weeks prior to the screening visit and between the screening and the baseline/randomization visit. In addition, patients must agree to switch to study-required prednisone/prednisolone as their OCS at visit 1 and use it per protocol for the duration of the study. The number of patients receiving OCS at baseline will be capped at approximately 25% of the study population.
•Must have experienced >=1 severe respiratory exacerbation requiring treatment with systemic corticosteroids or hospitalization or treatment in ED/urgent care within 12 months prior to the screening visit, or must have received systemic corticosteroids during 5 of the 6 months prior to the screening visit and between the screening and baseline visits.be receiving chronic stable low-dose OCS

NOTE: Other protocol defined inclusion criteria apply

Exclusion criteria

•Weight less than 30.0 kilograms
• Current smoker or e-cigarette user, cessation of smoking or e-cigarette use within 6 months prior to randomization, or >10 pack-years smoking history
•Post-bronchodilator FEV1 <30% predicted normal at screening
•For those receiving OCS at baseline: Considered to be at high risk for adverse events due to tapering of OCS, in the opinion of the investigator
• Respiratory exacerbation requiring systemic corticosteroids within 4 weeks prior to screening and between screening and baseline visit (for patients on daily or alternate day OCS, exacerbation requiring at least double the maintenance dose of corticosteroids)
• Upper or lower respiratory tract infection within the 4 weeks prior to screening (visit 1) or between the screening and randomization visits
• Significant chronic pulmonary disease other than asthma complicated with ABPA (eg, physician-diagnosed bronchiectasis due to a condition other than ABPA or with a history of a positive lower respiratory culture for P aeruginosa or other multi-drug-resistant, gram-negative bacilli; cystic fibrosis; sarcoidosis; interstitial lung disease not due to ABPA; chronic obstructive pulmonary disease [COPD] not due to ABPA; hypereosinophilic syndrome; etc) or a diagnosed pulmonary or systemic disease associated with elevated peripheral eosinophil counts
• Diagnosis or suspected diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA; also called Churg-Strauss Syndrome)

NOTE: Other protocol defined exclusion criteria apply

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:	Pending
Start date (anticipated):	12-10-2020
Enrollment:	6
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Dupixent (Dupilumab)
Generic name:	n/a
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	23-06-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-11-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-06-2021

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-11-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-04-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	27-11-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389

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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	EUCTR2019-002619-24-NL
CCMO	NL73438.018.20