A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Study to Assess the Efficacy, Safety and Tolerability, and Pharmacokinetics of INS1007 Administered Once Daily for 24 Weeks in Subjects with Non-Cystic Fibrosis Bronchiectasis - The Willow Study

Published: 29-11-2017
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Primary Objective:To evaluate the effect of INS1007 compared with placebo on time to first pulmonary exacerbation over the 24-week treatment period.Secondary Objectives:1. To evaluate the effect of INS1007 compared with placebo on quality of life (...

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

Summary

ID

NL-OMON48711

Source
ToetsingOnline

Brief title
Willow study

Condition

- Bronchial disorders (excl neoplasms)

Synonym
Non-Cystic Fibrosis Bronchectasis - Lung disease

Research involving
Human

Sponsors and support

Primary sponsor: Insmed Incorporated
Source(s) of monetary or material Support: Industry

Intervention

Keyword: Efficacy/safety INS1007, Non-Cystic Fibrosis Bronchectasis

Outcome measures

Primary outcome

The primary endpoint is the time to the first pulmonary exacerbation over the

24-week treatment period.

A pulmonary exacerbation in this study is defined as having 3 or more of the

following symptoms for at least 48 hours resulting in a physician*s decision to

prescribe antibiotics:

1 Increased cough;

2 Increased sputum volume or change in sputum consistency;

3 Increased sputum purulence;

4 Increased breathlessness and/or decreased exercise tolerance;

5 Fatigue and/or malaise;

6 Hemoptysis.

Subjects on chronic macrolide therapy whose only change in therapy is dose or

frequency adjustment will not meet the definition of exacerbation.

Secondary outcome

Secondary Endpoints:

1. Change from Baseline in QOL-B Respiratory Symptoms Domain score over the 24-week treatment period.

2. Change from Screening in post-bronchodilator FEV1 over the 24-week treatment period.

3. Change in concentration of active NE in sputum from pre-treatment (defined as the average of Screening and Day 1 concentrations) to on-treatment (defined as the average of Week 12 and Week 24 concentrations).

4. Rate of pulmonary exacerbations (number of events per person-time) over the 24-week treatment period.

Safety Endpoints:

The safety endpoints will include AEs, 12-lead ECG measurements, clinical laboratory testing results, vital sign measurements, physical examination results, and PFT measurements. Adverse events of special interest (AESIs) which will be reported include hyperkeratosis, periodontitis/gingivitis, and other infections.

Pharmacokinetic Endpoints:

The PK parameters, as estimated using non-compartmental analysis methods, will include maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), average plasma concentration at steady state (Css), maximum plasma concentration at steady state (Cmaxss), time to maximum plasma concentration at steady state (Tmaxss), minimum plasma concentration at steady state (Cminss), and area under the plasma concentration curve from 0 to 8 hours (AUC0-8).

Study description

Background summary

Bronchiectasis is a disease characterized by localized, irreversible enlargement of bronchi and bronchioles that may lead to obstructed breathing caused by abnormal mucus production. Bronchiectasis symptoms typically include a chronic dry or wet cough. Other symptoms include shortness of breath, coughing up blood, and chest pain. Wheezing and nail clubbing may also occur. People with the disease often get frequent lung infections.
Subjects having NCFBE experience pulmonary exacerbations with an average frequency ranging from 1.5 to 6 per year. Currently, there is no standard-of-care for prophylactic pharmacological treatment of NCFBE. The primary goal of treatment is to treat the underlying cause, prevent disease progression, maintain or improve lung function, and improve the symptoms and quality of life.

INS1007 is a potent, selective, competitive and reversible DPP1 inhibitor that was shown to inhibit the formation of all 3 active NSPs in maturing neutrophils in vitro and in vivo.

It is hypothesized that the functional inhibition of NSPs by a DPP1 inhibitor such as INS1007 will decrease inflammation and mucus hypersecretion, leading to slowing down lung tissue destruction, and decreasing the exacerbation rate in subjects with neutrophilic lung conditions with a protease-driven pathology such as NCFBE.
This study will evaluate whether this hypothesis is confirmed.

It is postulated that administration of INS1007 may result in beneficial effects for patients suffering from NCFBE via decreasing inflammation and mucus

hypersecretion, leading to an improvement in respiratory symptoms (eg, cough and sputum production) and lung function (eg, FEV1) and a decrease in exacerbation rate. Since INS1007 acts upstream of NE and inhibits two other NSPs regulated by DPP1, it may have a larger impact on slowing lung damage progression in NCFBE patients compared to inhibition of NE alone.
Considering the potential benefits to subjects with NCFBE, all the available data for INS1007 from the nonclinical toxicity studies, the 2 Phase 1 studies, and the risk mitigation strategies to be put in place, this study, in the opinion of the Sponsor, is considered to have a favorable risk-benefit ratio.

Study objective

Primary Objective:
To evaluate the effect of INS1007 compared with placebo on time to first pulmonary exacerbation over the 24-week treatment period.

Secondary Objectives:
1. To evaluate the effect of INS1007 compared with placebo on quality of life (QOL), as assessed by the Quality of Life Questionnaire-Bronchiectasis (QOL-B), Respiratory Symptoms Domain score, over the 24-week treatment period.

2. To evaluate the effect of INS1007 compared with placebo on lung function, as measured by forced expiratory volume in 1 second (FEV1), over the 24-week treatment period.

3. To evaluate the effect of INS1007 compared with placebo on the concentration of active neutrophil elastase (NE) in sputum, as measured by the difference between the pre-treatment concentration and on-treatment concentration.

4. To evaluate the effect of INS1007 compared with placebo on the rate of pulmonary exacerbations over the 24-week treatment period.

Safety Objective:
To assess the safety and tolerability of INS1007 relative to placebo based on adverse events (AEs), vital signs and electrocardiogram (ECG) measurements, physical exams, pulmonary function tests (PFTs), and clinical laboratory evaluations.

Pharmacokinetic Objectives:
1. To evaluate the pharmacokinetics (PK) of INS1007.

2. To assess the relationship between PK measures for INS1007 and efficacy, safety and biomarker measures (eg, concentrations of active NE in sputum and reagent-stimulated blood).

Study design

This is a Phase 2, randomized, double-blind, placebo-controlled, parallel-group, multicenter, multi-national study to assess the efficacy, safety and tolerability, and PK of INS1007 administered once daily (QD) for 24 weeks in subjects with non-cystic fibrosis bronchiectasis (NCFBE).

This multi-center study will be conducted at approximately 120 sites; enrollment is competitive across all sites. Across these sites, it is planned to randomize approximately 240 subjects with NCFBE. Subjects will be randomized in a 1:1:1 ratio to 3 treatment arms (80/arm) to receive either 10 mg or 25 mg of INS1007 or matching placebo. Randomization will be stratified based on whether the Screening sputum is culture positive for P aeruginosa and whether the subject is on a maintenance use of macrolides for preventing pulmonary exacerbation.

There will be a screening period of up to 6 weeks per subject. During the screening period, the subject*s demographic information, medical history, and smoking history will be obtained, a physical exam will be performed and the vital signs will be evaluated and a sputum sample for sputum culture will be collected. Biomarkers will be collected, and clinical laboratory test, pregnancy test, ECG, pulmonary function test (PFT), and periodontal cleaning and examination will be conducted. Subjects whose past chest radiographic image records are not available will undergo a chest CT scan during screening (Visit1). Subjects who meet all the inclusion but none of the exclusion criteria, except for the dental exclusion criteria, will proceed to have a dental examination for dental criteria screening. Subjects who meet all eligibility criteria will undergo a periodontal cleaning procedure prior to randomization.

Subjects will be randomized at Visit 2 (Day 1) and return thereafter for study visits at 2 (Visit 3), 4 (Visit 4), 8 (Visit 5), 12 (Visit 6), 16 (Visit 7), 20 (Visit 8), 24 (Visit 9) and 28 (Visit 10) weeks. There will be a visit window of ± 3 days for each of the scheduled visits. During each visit, all assessments and procedures will be performed as described in Section 6 of this protocol. Study treatment will occur between Visits 2 and 9.
Subjects will be required to have an end-of-study visit (Visit 10) at Week 28 to collect blood and sputum samples for biomarker assessment and to collect information on AEs and concomitant medications use. A PK sample will be collected from each subject participating in the PK sub-study.

Pharmacokinetic Sub-study:
A PK sub-study will be conducted at a select number of sites (NLD will not participate). Subjects who enroll at the selected sites will undergo intensive PK sampling. A maximum of 36 subjects will be included in the PK sub-study. For subjects who participate in the PK sub-study, the visit window for Visit 4 will be ± 5 days. Additionally, for subjects not participating in the PK sub-study, sparse PK sampling will be conducted in subjects at all sites with PK sampling processing capabilities. (see Section 7.6.1). Pharmacokinetic samples will be

analyzed in batches on an ongoing basis.

Intervention

Each subject will receive study treatment for 24 weeks. The entire study is scheduled to take a maximum of 32 weeks for each individual subject from Screening (Visit 1) to the End of Study (Visit 10).

Study burden and risks

Bronchiectasis is a disease with symptoms like a chronic dry or wet cough, shortness of breath, coughing up blood, chest pain, wheezing and often frequent lung infections. Subjects having NCFBE experience pulmonary exacerbations with an average frequency ranging from 1.5 to 6 per year. Currently, there is no standard-of-care for prophylactic pharmacological treatment of NCFBE. The primary goal of treatment is to treat the underlying cause, prevent disease progression, maintain or improve lung function, and improve the symptoms and quality of life.

It is expected that administration of INS1007 may result in beneficial effects for patients suffering from NCFBE via decreasing inflammation and mucus hypersecretion, leading to an improvement in respiratory symptoms (eg, cough and sputum production) and lung function (eg, FEV1) and a decrease in exacerbation rate. Since INS1007 acts upstream of NE and inhibits two other NSPs regulated by DPP1, it may have a larger impact on slowing lung damage progression in NCFBE patients compared to inhibition of NE alone.

Considering the potential benefits to subjects with NCFBE, all the available data for INS1007 from the nonclinical toxicity studies, the 2 Phase 1 studies, and the risk mitigation strategies to be put in place, this study, in the opinion of the Sponsor, is considered to have a favorable risk-benefit ratio.

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

Subjects who have given their signed, informed consent, are male or female between 18 and 85 years of age (inclusive) with a body mass index > 18.5 at Screening (Visit 1) and have a clinical history consistent with NCFBE will be eligible for enrollment in the study.

Exclusion criteria

Subjects who have a primary diagnosis of chronic obstructive pulmonary disease or asthma, have bronchiectasis due to cystic fibrosis, hypogammaglobulinemia, common variable immunodeficiency, or *1-antitrypsin deficiency, are current smokers as defined per Centers for Disease Control and Prevention criteria, or currently being treated for a non tuberculous mycobacterial lung infection, allergic bronchopulmonary aspergillosis, tuberculosis or have a clinical diagnosis of Papillon-Lefèvre Syndrome will not be eligible for enrollment in the study.

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:	Completed
Start date (anticipated):	16-08-2018
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	INS1007
Generic name:	INS1007

Ethics review

Approved WMO Date:	29-11-2017
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	26-04-2018
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	14-06-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	28-06-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-08-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-09-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-11-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-04-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-05-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2017-002533-32-NL
ClinicalTrials.gov	NCT03218917
CCMO	NL63023.100.17

Study results

Date completed: 14-11-2019

Results posted: 08-10-2020

First publication
08-07-2020