An Open-Label Safety Extension Study to a Multicenter Study of Liposomal Amikacin for Inhalation (LAI) in Adult Patients with Nontuberculous Mycobacterial (NTM) Lung Infections caused by Mycobacterium avium complex (MAC) That are Refractory to Treatment

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Primary Objective To evaluate long term safety and tolerability of LAI (590 mg) administered once daily (QD) for up to 12 months in subjects who were refractory to standard multi-drug treatment and failed to convert in Study INS-212. Secondary...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Mycobacterial infectious disorders
Study type	Interventional

Summary

ID

NL-OMON43501

Source
ToetsingOnline

Brief title
INS-312

Condition

- Mycobacterial infectious disorders
- Respiratory tract infections

Synonym

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Lung infection, Mycobacterial Lung Infection

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Amikacin, Liposomal, Mycobacterial infection

Outcome measures

Primary outcome

PRIMARY ENDPOINT - SAFETY

The primary endpoint is the frequency of treatment-emergent adverse events (TEAEs), TEAEs leading to withdrawal from study, treatment-emergent serious adverse events (SAEs), AEs of special interest, clinically significant abnormal laboratory test results, and vital signs measurements. The primary endpoint will evaluate the overall population and describe the subjects by treatment arm assigned in the INS-212 study (LAI added to a multi-drug regimen arm and a multi-drug regimen alone).

Secondary outcome

SECONDARY ENDPOINTS - EFFICACY

The secondary endpoints will evaluate the overall population and describe the subjects by treatment arm assigned in the INS-212 study (LAI added to a multi-drug regimen arm and a multi-drug regimen alone).

1. Proportion of subjects achieving culture conversion (3 consecutive monthly negative sputum cultures without relapse or recurrence) by Month 12/EOT.

2. Proportion of subjects achieving culture conversion by Month 6.

3. Time to culture conversion. The date of conversion is defined by the date of

the first of at least 3 consecutive monthly culture specimens that are MAC

negative.

4. The mean change from Baseline in 6MWT distance at Month 6 and Month 12/EOT

Study description

Background summary

Nontuberculous mycobacteria are ubiquitous in the environment. The pulmonary infection caused by these organisms
has features that overlap with tuberculosis, but disease definition can be more complex as recovery of a single isolate
from the airway secretions does not necessarily indicate disease. In contrast to tuberculosis, there is no convincing
evidence of person-to-person spread. It appears that the prevalence of human disease attributable to these organisms
over the past 2 decades is increasing. Pulmonary disease due to NTM was traditionally reported as primarily upper
lobe fibrocavitary disease occurring in male smokers with emphysema. More recently, certain disease and
demographic populations seem to be particularly susceptible to nodular bronchiectatic pulmonary disease with
predominant infection of the anterior aspect of the mid-lung.
Current treatment of NTM lung infection is primarily with multi-drug regimens developed for the treatment of
tuberculosis. This approach is not optimal, and the morbidity and mortality associated with NTM infection is significant.
A study demonstrated that mortality after 5 years in those who were infected according to the ATS/IDSA criteria was
40%.
The ongoing INS-212 study has been designed to evaluate whether the signal identified in a previous study is further confirmed in a longer duration of LAI treatment. Study INS-312 is an open-label safety extension to the INS-212 study that will further evaluate the safety and tolerability of once daily dosing of 590 mg LAI added to a multi-drug regimen in subjects with MAC lung infections that are refractory to therapy.

Study objective

Primary Objective
To evaluate long term safety and tolerability of LAI (590 mg) administered once daily (QD) for up to 12 months in subjects who were refractory to standard multi-drug treatment and failed to convert in Study INS-212.

Secondary Objectives
1.To evaluate the number of subjects achieving culture conversion (3 consecutive monthly negative sputum cultures) by Month 12/EOT (end of treatment).
2.To evaluate the number of subjects achieving culture conversion by Month 6.
3.To evaluate the time to culture conversion.
4.To evaluate the change in the six-minute walk test (6MWT) distance at Month 6 and Month 12/EOT.

Exploratory Objectives
1.To assess subject-reported symptoms of NTM and change from Baseline in quality of life scores on the St George*s Respiratory Questionnaire (SGRQ) and quality of life scores on the SGRQ * Part II (Activities of Daily Living) at Month 6 and Month 12/EOT
2.To assess the change from Baseline in the EQ-5D-3L questionnaire subject-reported health outcomes at Month 6 and Month 12/EOT.

Study design

Eligible subjects will have successfully completed their Month 6 visit in the INS-212 study. At the scheduled Month 8 visit, eligible subjects will be confirmed to have not achieved the INS-212 protocol definition of culture conversion or to have experienced a relapse or recurrence. The scheduled Month 8 visit will become the EOT visit. Subjects will enroll directly from the INS-212 study at their EOT visit after having met all eligibility criteria for the INS-312.
Subjects will receive LAI 590 mg administered QD added to a multi-drug regimen for 12 months. All subjects will return 1 month after EOT for an off LAI treatment follow-up visit at the end of study (EOS) visit.
All subjects will have routine visits at Day 1, Months 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12/EOT. All subjects will return 1 month after EOT for an off LAI treatment follow-up visit (EOS).

Intervention

LAI will be supplied by Insmed Incorporated in clear glass 10 mL vials for nebulization for a delivered dose of 590 mg. The study drug will be administered via inhalation using the PARI Pharma GmbH eFlow® nebulizer (eFlow® nebulizer), a small machine that delivers medication in the form of a mist inhaled into the lungs, which is approved by the European Medicines Agency for use in the European Union (elsewhere it is an investigational medical device

that is not yet commercially approved).
Study drug will be administered QD. Subjects who develop bronchospasm may be pre-treated with a bronchodilator before study drug administration. Subjects who were pre-treated with a bronchodilator in the INS-212 study should continue to be pre-treated in the INS-312 study.

Study burden and risks

The most common side effects of LAI are cough, joint pain, mild-to-moderate hoarseness or loss of voice, feeling sick,
throat pain and irritation, throat tightness, cough producing mucous, fever, runny nose, wheezing, sinus issues,
headache, coughing up blood, sore throat, shortness of breath, ringing in the ears, feeling tired, chills, bitter taste in the
mouth, the loss of balance and shivering.
There may be other risks that are unknown that we cannot predict.
Other potential side-effects includes the risks associated with blood sampling, hearing test and electrocardiogram.
More detailed information may be found in the Patient Information Sheet.

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 are eligible to participate in the study if they meet all the following inclusion criteria:
1. have successfully completed the Month 6 and EOT visits in INS-212
2. have not achieved the INS-212 protocol definition of culture conversion (3 consecutive monthly negative sputum cultures) by Month 6 in INS-212
OR
have experienced a relapse or recurrence (agar positive or more than 2 consecutive broth positive results after culture conversion has occurred) by Month 6 in INS-212
3. have demonstrated compliance with treatment regimen in INS-212, including LAI, if applicable
4. willing to adhere to multi-drug treatment regimen during the course of the study
5. female of child bearing potential agrees to practice an acceptable method of birth control (e.g., true abstinence [refraining from heterosexual intercourse during the study], hormonal or barrier
methods, partner sterilization, or intrauterine device [IUD]) while participating in the trial. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception.
6. the subject will provide written informed consent
7. willing to have serum and sputum specimens stored
8. able to comply with study drug use, study visits, and study procedures as determined by the Investigator

Exclusion criteria

Subjects are not eligible to participate in the study if they meet any of the following criteria:
1. achieved culture conversion without relapse or recurrence in the INS212study by Month 6
2. early discontinuation (prior to Month 6 study visit) from INS-212
3. met any of the exclusion criteria of the INS-212 study, with the exception of the following:
a. unable to perform the 6MWT
b. prior exposure to LAI (including clinical study)
c. in the opinion of the Investigator, patients who are not expected to survive the duration of the study
d. active allergic bronchopulmonary mycosis or any other condition requiring chronic systemic corticosteroids at a dose greater than the equivalent of 10 mg/day of prednisone within 3 months before Baseline (Day 1)

e. initiation of chronic therapy (e.g., high dose ibuprofen, inhaled anti-inflammatory agents including steroids, low dose maintenance steroids, rhDNase) at Baseline (Day 1)
4. positive pregnancy test or lactation. All women of child bearing potential will be tested. Women not of child bearing potential are defined as postmenopausal (i.e., amenorrheic for at least 1 year), or surgically or naturally sterile.
5. significant (as determined by the Investigator) hearing loss, vestibular dysfunction, or neuromuscular weakness where the potential risk of aminoglycoside toxicity outweighs the potential benefit
6. aspartate aminotransferase or alanine aminotransferase * 3 times the upper limit of normal (ULN) and/or total bilirubin * 2 times the ULN at their Month 6 study visit in INS-212
7. absolute neutrophil count *500/*L at their Month 6 study visit in INS2128. serum creatinine >2 times ULN at their Month 6 study visit in INS-212
9. current alcohol, medication abuse, or illicit drug abuse
10. any condition that, in the opinion of the Investigator, interferes with ability to safely complete the study or adhere to study requirements
11. diagnosis of myasthenia gravis

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-06-2016
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Liposomal Amikacin for Inhalation
Generic name:	Liposomal Amikacin for Inhalation

Ethics review

Approved WMO Date:	24-02-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-05-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-06-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-06-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-11-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-11-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-01-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-01-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-04-2017

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-07-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-07-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-07-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-08-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-09-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2015-003170-33-NL
ClinicalTrials.gov	NCT02628600
CCMO	NL55888.091.16

Study results

Date completed: 19-07-2017

Actual enrolment: 1

Summary results
Trial is onging in other countries