A Randomized, Open Label, 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

Published: 01-04-2015
Last updated: 14-04-2024

Primary Objective1. To evaluate the efficacy of LAI (590 mg) administered once daily (QD), when added to a multi-drug regimen, for achieving culture conversion (3 consecutive monthly negative sputum cultures) by Month 6 compared to a multi-drug...

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

Summary

ID

NL-OMON43943

Source
ToetsingOnline

Brief title
INS-212

Condition

- Mycobacterial infectious disorders
- Respiratory tract infections

Synonym

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

The primary endpoint is the proportion of subjects achieving culture conversion (3 consecutive monthly negative sputum cultures) by Month 6 in the LAI arm compared to multi-drug regimen alone.

Secondary outcome

1. Change in 6MWT distance at Month 6 in the LAI arm compared to a multi drug regimen alone

2. Proportion of subjects achieving culture conversion with durability after 3 months off treatment in the LAI arm compared to a multi drug regimen alone

3. Time to culture conversion in the LAI arm compared to a multi drug regimen alone by Month 6

4. Proportion of subjects achieving culture conversion with sustainability at the EOT in the LAI arm compared to a multi drug regimen alone

5. Change in 6MWT distance at EOT in the LAI arm compared to a multi drug regimen alone

6. Change from Baseline (Day 1) at Month 6 in the SGRQ.

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%.

Study objective

Primary Objective
1. To evaluate the efficacy of LAI (590 mg) administered once daily (QD), when added to a multi-drug regimen, for achieving culture conversion (3 consecutive monthly negative sputum cultures) by Month 6 compared to a multi-drug regimen alone

Secondary Objectives
1. To evaluate the efficacy of LAI (590 mg) administered QD when added to a multi drug regimen on the six minute walk test (6MWT) at Month 6 compared to a multi drug regimen alone
2. To evaluate the efficacy of LAI (590 mg) QD when added to a multi drug regimen on the durability of treatment success 3 months after the end of total treatment course (negative sputum culture after 3 months off treatment)
3. To evaluate the efficacy of LAI (590 mg) administered QD when added to a multi drug regimen for time to culture conversion compared to a multi drug regimen alone
4. To evaluate the efficacy of LAI (590 mg) administered QD, when added to a multi drug regimen, for achieving sustainability (consecutive negative sputum cultures [with no more than 2 consecutive monthly broth positive cultures] for 12 months on treatment) compared to a multi drug regimen alone

5. To evaluate the efficacy of LAI (590 mg) administered QD when added to a multi drug regimen on the 6MWT at End of Therapy (EOT) compared to a multi drug regimen alone
6. To evaluate patient reported symptoms of NTM and change from Baseline (Day 1) in quality of life scores on the St. George*s Respiratory Questionnaire (SGRQ) at Month 6

Exploratory Objectives
1. To evaluate the change from Baseline to Month 6 on the 6MWT for converters versus non-converters within the LAI (590 mg) administered QD added to a multi-drug regimen arm
2. To evaluate the change from Baseline to Month 6 on the 6MWT for converters versus non-converters for all subjects
3. To evaluate the change from Baseline to Month 6 on the 6MWT for converters versus non-converters within the multi-drug regimen alone arm
4. To evaluate the change from Baseline to Month 6 on Body Mass Index (BMI) for those randomized to LAI (590 mg) administered QD added to a multi drug regimen compared to a multi drug regimen alone
5. To evaluate the efficacy of LAI (590 mg) administered QD when added to a multi drug regimen on the 6MWT at Month 8 and 3 months off-treatment compared to a multi drug regimen alone
6. To evaluate the proportion of subjects achieving culture conversion with durability after 12 months off treatment (EOS) in the LAI arm compared to a multi drug regimen alone
7. To compare patient reported symptoms of NTM and change from Baseline (Day 1) in quality of life scores on the SGRQ * Part 2 (Activities of Daily Living) at Month 6
8. To compare change from Baseline (Day 1) in the EQ-5D-3L patient reported health outcomes at Month 6 and EoT
9. To evaluate the number of subjects in each treatment arm who develop a new strain of MAC during the study at EOS
10. To compare all cause mortality between treatment arms 12 months after treatment (EOS)

Safety objective
1. To evaluate the safety and tolerability of LAI (590 mg) QD added to a multi-drug regimen arm

Pharmacokinetic Objectives
1. To evaluate the pharmacokinetics (PK) of LAI via a population PK approach
2. To evaluate the concentration of amikacin in sputum after days interruption of LAI dosing in a subset of subjects
3. To evaluate the concentration of amikacin in sputum after 28 days off-LAI in a subset of subjects
4. To evaluate the concentration of amikacin in sputum after 3 months off-LAI in a subset of subjects

Study design

The Screening window allows time for sputum culture results, susceptibility by minimum inhibitory concentration (MIC) determination, and scheduling of Screening assessments. Any delay in obtaining microbiological results and MICs must be reported to the Sponsor immediately and documented within the study source documents. In the event that sputum culture results are not known by 8 weeks (Day -14), the Baseline (Day 1) visit should be scheduled as soon as possible in order to maintain the Screening window, and an extension of the Screening window to 14 weeks is allowed, if necessary. If sputum culture results are known prior to 8 weeks (Day -14), the Screening window of 10 weeks must be maintained. Once Screening assessments are complete and sputum culture results are known, eligible subjects will be randomized 2:1 to LAI administered QD plus a multi-drug regimen or a multi-drug regimen alone. The primary efficacy endpoint is the proportion of subjects achieving culture conversion (3 consecutive monthly negative sputum cultures by Month 6 in the LAI plus a multi-drug regimen arm compared to a multi-drug regimen alone.

Converters are defined as subjects who have 3 consecutive monthly MAC-negative sputum cultures at any time within the first 6 months of the study. After culture conversion, relapse or recurrence is defined as having MAC-positive sputum cultures in liquid broth media (agar negative) for 3 or more consecutive months, or having 1 MAC-positive sputum culture on solid media (agar positive). Non-converters are defined as subjects who do not have 3 consecutive monthly MAC-negative sputum cultures at any time within the first 6 months of the study. Sputum culture results will only be available to the site after the Month 6 sputum result is known, in time for the Month 8 visit. At Month 8 (-28 to +7 days), after all sputum culture results are known, up to and including Month-6, subjects will be assessed as converters or non converters.

All converters will remain in Study INS-212. All converters who, after culture conversion, subsequently have MAC-positive sputum cultures in liquid broth media (agar negative) for 1 or 2 consecutive months only, will also remain in Study INS-212.
These subjects will continue on their randomized treatment regimen until they complete a total of 12 months of treatment (EOT), starting from the first of 3 negative cultures that defines culture conversion. These subjects will return after the EOT visit for 28 day, 3, 6 and 12 months off-treatment follow-up visits. The 12 months off-treatment follow-up visit will be the end of study (EOS) visit. No NTM treatment will be administered during the off-treatment phase.

At Month 8, all non-converters will be discontinued from INS-212. All subjects who experienced a relapse or recurrence after culture conversion by Month 6 will also be discontinued from INS-212 at their Month 8 visit. These subjects may be eligible to enter a separate open-label study of LAI (Study INS-312),

provided all entry criteria have been met for that study.
Expectorated sputum (spontaneous or induced e.g., with nebulized hypertonic saline solution as needed) will be collected at Day 1 and every month through Month 6, at Month 8, Month 12, EOT, and at 28 days, 3, 6, and 12/EOS months off-treatment.
All subjects will come in monthly for routine visits through Month 6, at Month 8, 10, 12, 14, EOT, and at 28 days, 3, 6 and 12/EOS months off-treatment. Home Healthcare visits may be available at Months 1, 2, and 5 for sites with IRB/EC approval to conduct Home Healthcare visits, and for qualifying subjects who may have difficulty attending clinic visits. Unscheduled visits will occur as needed should subject*s symptoms worsen between visits.

Intervention

Group 1 : multi-drug therapy and 590 mg LAI for 16 months. The study drug will be administered via inhalation using the PARI eFlow® nebulizer (eFlow®). Study drug will be administered QD except on days to provide sputum before the site visits.

Group 2 : multi-drug therapy (SOC) for 16 months.

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.

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

1. be male or female, 18 years or older (20 years or older in Japan)
2.be positive for MAC on culture as defined in inclusion criterion No. 4 while being treated with a multi-drug treatment regimen (at least 2 antibiotics) for a minimum duration of 6 consecutive months that is either ongoing or was stopped no more than 12 months before Screening (exceptions to multi-drug treatment regimen for 6 consecutive months include treatment with doses or frequencies below those recommended by guidelines and/or short interruptions of therapy, both occurring due
to safety/tolerability issues)
3. be diagnosed with MAC NTM lung infection with evidence of underlying lung disease such as nodular bronchiectasis and/or fibrocavitary disease by chest radiography (CXR) or high-resolution
chest computed tomography. High resolution CT (HRCT) scan is preferred, if available
4. have a MAC lung infection documented by at least 2 positive cultures (MAC or mixed infection with MAC as the dominant species), consisting of at least one positive culture obtained within 6 months prior to Screening and one positive culture at Screening (cultures to be at least 1 month apart). Cultures may be obtained from sputum or bronchoscopy.
5. have a MAC-positive sputum at screening
6. be willing to adhere to multi-drug treatment regimen during the course of the study
7. be able to produce approximately 3 mL of sputum or be willing to undergo an induction that produces approximately 3 mL of sputum for mycobacteriology
8. female of child bearing potential agrees to practice an acceptable method of birth control (e.g., true abstinence [refraining from heterosexual intercourse during the entire 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.
9. the patient will provide written informed consent before performing any study related procedure
10. be willing to have serum specimens stored
11. be able to comply with study drug use, study visits, and study procedures as determined by the investigator

Exclusion criteria

A patient with any of the following conditions must be excluded from this study:
1. patients with cystic fibrosis
2. patients whose MAC NTM infection is resistant to amikacin (as identified by MIC susceptibility > 64µg/ml)
3. patients who are not able to perform the 6MWT
4. positive pregnancy test or lactation at Screening. All women of child bearing potential will be tested. Women not of childbearing potential are defined as postmenopausal (i.e., amenorrheic for at least 1 year), or surgically or naturally sterile.
5. active pulmonary malignancy (primary or metastatic) or any malignancy requiring chemotherapy or radiation therapy within 1 year before Screening or anticipated during the study period
6. 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 Screening
7. active pulmonary tuberculosis requiring treatment at Screening
8. history of lung transplantation
9. initiation of chronic therapy (e.g., high dose ibuprofen, inhaled anti inflammatory agents including steroids, low dose maintenance steroids, recombinant human deoxyribonuclease [rhDNase]) within 28 days before Day 1.
10. administration of any investigational drug within 8 weeks before Screening
11. prior exposure to LAI (including clinical study).
12. known hypersensitivity to aminoglycosides
13. use of inhaled or systemic aminoglycosides with activity against MAC (e.g., amikacin, kanamycin, or streptomycin) within 28 days before Day 1
14. acquired and primary immunodeficiency syndromes and acquired immunodeficiency syndromes (e.g. HIV-positive patients regardless of CD4 counts)
15. significant (as determined by the Investigator) hearing loss, vestibular dysfunction, neuromuscular weakness or a diagnosis of myasthenia gravis where the potential risk of aminoglycoside toxicity outweighs the potential benefit
16. aspartate aminotransferase or alanine aminotransferase * 3 times the upper limit of normal (ULN) or total bilirubin * 2 times the upper limit of normal (ULN) at Screening
17. absolute neutrophil count *500/*L at Screening
18. serum creatinine >2 times ULN at Screening
19. current alcohol, medication or illicit drug abuse
20. any condition that, in the opinion of the Investigator, interferes with ability to safely

complete the study or adhere to study requirements
21. persons who have been committed to an institution by virtue of an order issued either by the judicial or the administrative authorities
22. in the opinion of the Investigator, patients who are not expected to survive the duration of the study
23. patients with disseminated MAC infection

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-08-2015
Enrollment:	8
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:	01-04-2015

Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-06-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-07-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-08-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-10-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-11-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-05-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-06-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-10-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-11-2016

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:	24-01-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-03-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-03-2017
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)

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	EUCTR2014-005010-31-NL
ClinicalTrials.gov	NCT02344004
CCMO	NL52261.091.15