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A first-in-human study of the safety and efficacy of a new drug, a gamma secretase inhibitor, to treat people with sensorineural hearing loss

Submission date
21/03/2017

Recruitment status
No longer recruiting

Registration date
16/05/2017

Overall study status
Completed

Last Edited
04/03/2024

Condition category
Ear, Nose and Throat

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Sensorineural hearing loss (SNHL) is caused by damage to the hair cells lining the inner ear. The hair cells in the inner ear play an important role in transmitting sounds to the brain. Up until now, damage to the inner ear hair cells has been considered irreversible. Once hair cells become damaged, they will remain damaged throughout a person's life. Hearing aids can be used for people with hearing loss to amplify sounds to make it easier for damaged hair cells to detect them but there is currently no cure. Recently, scientists have made discoveries in animals which show that it is possible to regrow hair cells, and potentially restore hearing loss, using a medication known as a gamma secretase inhibitor. The aim of this study is to test a new drug that may be able to treat sensorineural hearing loss (SNHL).

Who can participate?
Adults aged 18 to 80 who have hearing loss.

What does the study involve?
This study involves two parts. In the first part of the study, participants have three treatments of LY 3056480 injected into one ear. At the first treatment visit, participants attend the hospital and receive a 25 µg dose and are asked to stay overnight to test their hearing, balance and health. Participants are followed up by telephone the next day and then six days after the treatment they return to the hospital to repeat the tests. The second treatment visit, participants receive another dose. Participants are allowed to go home after and receive follow up telephone call one day after treatment. They are asked to return to the hospital six days after the return to repeat the tests. The third treatment visit, participants receive another dose. Participants are allowed to go home after and receive follow up telephone call one day after treatment. They are asked to return to the hospital six days after the return to repeat the tests. If participants find their maximum tolerated dose (MTD) then they are enrolled in the second part of the study. Participants are then randomly allocated to receive either the MTD or one dose below, using the same process as the first part of the study.

What are the possible benefits and risks of participating?
Participants may benefit from improvements to their hearing loss symptoms. There are always risks involved in testing new drug treatments in people. As this is the first time the drug is tested in humans, it is not clear what the exact risks will be, but specific functions like hearing and tinnitus, balance, facial nerve function and taste are monitored closely for any changes throughout the study. In addition, side effects occurring elsewhere, including the site of the injection in the ear, the heart, kidneys and liver and blood are checked.

Where is the study run from?
Ear Nose and Throat Hospital UCL (UK)

When is the study starting and how long is it expected to run for?
July 2016 to December 2019 (as of 18/10/2018)

Who is funding the study?
Horizon 2020 Framework Programme (Belgium)

Who is the main contact?
Mr Rolf Jan Rutten
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Contact information

Type(s)
Public

Contact name
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Additional identifiers

EudraCT/CTIS number
2016-004544-10

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
AUT-001

Study information

Scientific Title
A Phase I/II multiple ascending dose open-label safety and efficacy study of the Notch Inhibitor LY3056480 in patients with mild to moderate SNHL

Acronym
REGAIN

Study objectives
LY3056480 may induce transdifferentiation of supporting cells into inner-ear hair cells and lead to a subsequent improvement of hearing in patients with sensorineural hearing loss (SNHL).

Ethics approval required
Old ethics approval format

Ethics approval(s)
London - Central REC Committee, 25/10/2017, ref: 17/LO/0632

Study design
Part 1: Open-label single centre multiple ascending dose safety study
Part 2: Multi-centre efficacy randomised study

Primary study design
Interventional

Secondary study design

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Sensorineural hearing loss

Interventions
In the first part of this study, participants have three treatment visits where they receive three injections of LY3056480 administered trans-tympanically into one ear. This is done using a location anaesthetic cream to numb the ear drum. The drug is injected through the eardrum using a syringe. This injection takes approximately ten minutes. This is done in ascending dose cohort of 25µg, 125µg, 200µg, and 250µg applied in 500 µl. The maximum dose is determined by the maximum volume that can be administered in the inner ear and the maximum solubility in

the formulation. For the selected starting dose a safety factor of ten is applied, starting with 10% of the maximum dose. Participants are asked to lay till with their head in a set position for one hour after receiving their injections.

At the first visit, participants receive a dosage of 25µg and stay overnight at the hospital in order to monitor their hearing, balance, and general health to assess the safety of the drug. Participants are monitored routinely for their blood pressure, heart rate, and oral temperature. After participants are assessed for their hearing, balance and general health they are discharged. Participants then receive a telephone call the day after the first study visit to check how they are feeling. Six days after the first treatment visit, participants return to the hospital to repeat the tests.

The second visit occurs seven days after the first visit. Participants return to the hospital and the injection is repeated (25µg). Participants are able to go home after they are assessed for hearing balance and general health. Participants receive a telephone call one day after treatment to see how they are feeling. Participants then return to the hospital six days after their second visit for a safety visit, which repeats some of the assessments.

The third study visit occurs seven days after the second study visit. Participants return to the hospital and the injection is repeated (25µg). Participants are able to go home after they are assessed for hearing balance and general health. Participants receive a telephone call one day after treatment to see how they are feeling. Participants then return to the hospital six days after their second visit for a safety visit, which repeats some of the assessments.

Participants receive two more follow up visits, six and 12 weeks after their first treatment visit. The follow up takes around half a day and assesses the safety of the new drug. The overall study takes around 14 weeks.

In the second phase of the study, participants receive the highest tolerable dose resulted from the first section of the study or one dose below the highest tolerable dose (if the Maximum Tolerated Dose MTD is reached in the first part of the study). This part is designed to establish efficacy parameters at the MTD but also allows us to possibly determine a potential dose-response effect. If the MTD is found, participants are randomly assigned to the MTD or the dose below the MTD. Injections are delivered in the same process as the first part of the study.

Intervention Type
Drug

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
LY3056480

Primary outcome measure
Part 1:
1. Occurrence and severity of procedure related local and systemic AEs are measured using clinical examinations, laboratory tests and patient interviews at visit one, two and three
2. Occurrence of systemic AEs as measured by potentially clinically significant changes by ECG, vital signs, physical examinations and laboratory tests at visit one, two and three
3. Occurrence of surgical and injection sites reactions in and around the treated ear as assessed

by otomicroscopy at visit one, two and three
4. Safety of the treatment is assessed using changes in hearing, facial nerve function and balance at visit one, two and three

Part 2:
Efficacy of local treatment is measured if an optimal dose is found in part 1.

Secondary outcome measures
1. Change in hearing is measured using Pure Tone Audiometry (PTA) (dBHL) at baseline and week 12
2. Balance is measured using several balance tests at visit one, two, and three
3. Tinnitus measured using a questionnaire at visit one, two and three

Overall study start date
01/07/2016

Completion date
31/12/2019

Eligibility

Key inclusion criteria
1. Male or female between 18 and 80 years of age
2. A primary complaint of hearing loss of 10 years in duration, the history suggesting this hearing-loss to be of age-related, noise-induced or idiopathic origin
3. A bilateral, symmetrical (<15 dBHL difference) SNHL with a pure-tone average threshold across the frequencies 0.5, 1, 2, 4 and 8 kHz of between 25 and 60 dBHL with 2 or more frequencies less than 60 dBHL

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
62

Total final enrolment
59

Key exclusion criteria
1. Presenting with a primary complaint of tinnitus
2. A ‘true’ air-bone gap >15 dBHL in 3 or more contiguous frequencies between 0.5, 1, 2, 4 kHz

3. History of suspected or diagnosed genetic cause of hearing loss
4. Suspected or known diagnosis of inner ear pathology, congenital hearing loss, fluctuating hearing loss, Ménière's disease, or secondary endolymphatic hydrops, perilymph fistula, cochlear barotrauma, autoimmune hearing loss, radiation-induced hearing loss, retro-cochlear lesion
5. Evidence of acute or chronic otitis media or otitis externa on examination; or a history of middle ear pathology and/or surgery
6. Any therapy known as ototoxic within 12 months of screening

Date of first enrolment
15/09/2017

Date of final enrolment
19/07/2019

Locations

Countries of recruitment
England

Germany

Greece

United Kingdom

Study participating centre
Ear Nose and Throat Hospital UCL
330 Grays Inn Road
Kings Cross
London
United Kingdom
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Study participating centre
University of Tübingen
Universitäts klinikum Tübingen
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Study participating centre
The National and Kapodistrian University of Athens
1st Department of Otolaryngology
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Greece
157 72

Sponsor information

Organisation
Audion Therapeutics BV

Sponsor details
Linnaeusparkweg 10-2
Amsterdam
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Sponsor type
Industry

Funder(s)

Funder type
Government

Funder Name
Horizon 2020 Framework Programme

Alternative Name(s)
EU Framework Programme for Research and Innovation H2020, Horizon 2020, Rahmenprogramm Horizont 2020, Programa Marco Horizonte 2020, Programme-cadre Horizon 2020, Programma quadro Orizzonte 2020, Program ramowy Horyzont 2020, Horizont 2020, Horizonte 2020, Orizzonte 2020, Horyzont 2020, Horizon 2020 Framework Programme (H2020), H2020

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Results and Publications

Publication and dissemination plan

Planned publication in a high-impact peer reviewed journal.

Intention to publish date
30/04/2020

Individual participant data (IPD) sharing plan
The current data sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results		22/10/2021	22/10/2021	No	No
Basic results	Corrected Basic Results file	23/10/2021	26/10/2021	No	No
HRA research summary			28/06/2023	No	No
Results article		01/03/2024	04/03/2024	Yes	No