# Clinical trial results:
# A phase I/II multiple ascending dose open-label safety and efficacy study of the Notch Inhibitor LY3056480 in patients with mild to moderate sensorineural hearing loss.

## Summary

| | |
|---|---|
| EudraCT number | 2016-004544-10 |
| Trial protocol | GB GR DE |
| Global end of trial date | 07 October 2020 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 31 March 2022 |
| First version publication date | 31 March 2022 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | AUT-001 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | ISRCTN59733689 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Audion Therapeutics BV |
| Sponsor organisation address | Hogeweg 54, Amsterdam, Netherlands, 1098CE |
| Public contact | Clinical Trial Information, Audion Therapeutics, 0031 o6 46767255, rjrutten@audiontherapeutics.com |
| Scientific contact | Clinical Trial Information, Audion Therapeutics, 0031 06 46767255, rjrutten@audiontherapeutics.com |

Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 16 July 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 07 October 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 07 October 2020 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The main objectives of this trial (Part B) are:
1. Main objective is to establish the efficacy of local treatment with LY3056480 in terms of hearing at 12 weeks;
2. To establish the efficacy of local treatment with LY3056480 in terms of hearing at 6 weeks;
3. To assess the safety and tolerance of local treatment with LY3056480

Protection of trial subjects:

Informed consent, insurance

Background therapy:

NA

Evidence for comparator:

NA

| | |
|---|---|
| Actual start date of recruitment | 08 November 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United Kingdom: 39 |
| Country: Number of subjects enrolled | Germany: 12 |
| Country: Number of subjects enrolled | Greece: 8 |
| Worldwide total number of subjects | 59 |
| EEA total number of subjects | 20 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |

| | |
|---|---|
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 44 |
| From 65 to 84 years | 15 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

From January 24 to October 17, 2018, 15 Phase I trial patients were enrolled at the UK site. From January 30 to August 5, 2019, 44 Phase IIa patients were enrolled in the UK (N=24), Germany (N=12) and Greece (N=8).

### Pre-assignment

Screening details:

In phase I 27 patients were screened, N = 12 were not enrolled (Eligibility criteria = 8, Sponsor decision = 2, Withdrew consent = 3).
In phase IIa 55 patients were screened, N = 11 were not enrolled (Eligibility criteria = 8, Withdrew consent = 3).

### Period 1

| | |
|---|---|
| Period 1 title | Study duration (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

NA

### Arms

| | |
|---|---|
| **Arm title** | LY3056480 |

Arm description:

In phase I three injections of LY3056480 were administered trans-tympanically into one ear. The patients were treated in ascending dose cohorts of 25µg, 125µg, 200µg and 250µg applied in a volume of 500 µl (sterile diluent).
In phase IIa patients received three injections of 250µg of LY3056480 applied in 500 µL.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | LY3056480 |
| Investigational medicinal product code | LY3056480 |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Transdermal use |

Dosage and administration details:

Three injections of LY3056480 were administered trans-tympanically into one ear.
The patients were treated with 25µg, 125µg, 200µg and 250µg applied in a volume of 500 µl (sterile diluent).

| **Number of subjects in period 1** | LY3056480 |
|---|---|
| Started | 59 |
| Completed | 42 |
| Not completed | 17 |
| Consent withdrawn by subject | 17 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Study duration (overall period) |
| Reporting group description: all subjects enrolled | |

| Reporting group values | Study duration (overall period) | Total | |
|---|---|---|---|
| Number of subjects | 59 | 59 | |
| Age categorical | | | |
| Age in years | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 44 | 44 | |
| From 65-84 years | 15 | 15 | |
| 85 years and over | 0 | 0 | |
| Adult | 0 | 0 | |
| elderly | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| median | 59 | | |
| full range (min-max) | 22 to 79 | - | |
| Gender categorical | | | |
| Gender (male or female) | | | |
| Units: Subjects | | | |
| Female | 22 | 22 | |
| Male | 37 | 37 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | LY3056480 |
| Reporting group description: | |
| In phase I three injections of LY3056480 were administered trans-tympanically into one ear. The patients were treated in ascending dose cohorts of 25µg, 125µg, 200µg and 250µg applied in a volume of 500 µl (sterile diluent).<br>In phase IIa patients received three injections of 250µg of LY3056480 applied in 500 µL. | |
| Subject analysis set title | Part B |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: | |
| analysis partB | |
| Subject analysis set title | week12 |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: | |
| week 12 | |

### Primary: PTA

| | |
|---|---|
| End point title | PTA |
| End point description: | |
| | |
| End point type | Primary |
| End point timeframe: | |
| 3 months | |

| End point values | LY3056480 | Part B | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 43 | 43 | | |
| Units: decibel | | | | |
| number (confidence interval 95%) | 0.44 (-2.01 to 1.13) | 0.44 (-2.01 to 1.13) | | |

### Statistical analyses

| Statistical analysis title | Mixed-effect model |
|---|---|
| Statistical analysis description: | |
| For Phase IIa we set a recruitment target of 40 patients, based on 87% power to detect a 10 dB(HL) change (standard deviation 20 dB(HL)) corresponding to an effect size of 0.5024. We performed exploratory analyses for all efficacy points of Phase IIa and subgroup analyses per trial site. A three-level linear mixed-effect model was used to account for repeated measures and the multilevel structure of the pure-tone audiometry and speech-in-noise data. | |
| Comparison groups | LY3056480 v Part B |

| | |
|---|---|
| Number of subjects included in analysis | 86 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | > 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| Variability estimate | Standard deviation |

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: From informed consent until month 12 | |
| Assessment type | Systematic |
| **Dictionary used** | |
| Dictionary name | MedDRA |
| Dictionary version | 21.1 |
| **Reporting groups** | |
| Reporting group title | LY3056480 |
| Reporting group description: all patients who have received at least 1 dose of LY3056480 | |

| Serious adverse events | LY3056480 | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 59 (3.39%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bladder tumor | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| broken shoulder | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | LY3056480 | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 57 / 59 (96.61%) | | |
| Ear and labyrinth disorders | | | |

| | | | |
|---|---|---|---|
| Injection site pain | Additional description: 49 of the 59 participants experienced injection site pain, 83% | | |
| subjects affected / exposed | 49 / 59 (83.05%) | | |
| occurrences (all) | 49 | | |
| Tinnitus | Additional description: 27 of the 59 participants experiened transient tinnitus (46%) | | |
| subjects affected / exposed | 27 / 59 (45.76%) | | |
| occurrences (all) | 27 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 01 June 2017 | see protocol |
| 17 July 2017 | see protocol |
| 20 March 2018 | see protocol |
| 04 December 2018 | see protocol |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported