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). 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