Clinical trial results:
A Balanced Randomised Placebo Controlled Double-blind Phase IIa Study to Investigate the Efficacy and Safety of AUT00063 Versus Placebo in Subjective Tinnitus

Summary

EudraCT number	2014-002179-27
Trial protocol	GB
Global end of trial date	02 December 2015

Results information

Result version number	v1 (current)
This version publication date	08 December 2016
First version publication date	08 December 2016

Trial information

Trial identification

Sponsor protocol code	AUT032063

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02315508
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Autifony Therapeutics Ltd
Sponsor organisation address	Imperial College Incubator, London, United Kingdom, SW7 2AZ
Public contact	Alice Grant, Autifony Therapeutics Limited, +44 (0)203 763 9477, alice.grant@autifony.com
Scientific contact	John Hutchison, Autifony Therapeutics Limited, john.hutchison@autifony.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	22 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 December 2015
Global end of trial reached?	Yes
Global end of trial date	02 December 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate a clinically- relevant improvement in tinnitus severity after repeat dosing in subjects with subjective tinnitus

Protection of trial subjects:

Before they were screened for the study, Investigators were responsible for informing all subjects of the study design, possible benefits, risks, and outcomes of the treatment, the test products used, and the insurance policy. Subjects were provided with the Ethics approved Participant Information Sheet and given time to consider their participation. Subjects had to provide written informed consent before they entered the study.
Safety assessments were conducted at Screening, pre- and post-dose on Day 1, Day 28 and Day 42 (two weeks after last dose). Subjects were also contacted on Day 14 to collect any adverse events and concomitant medications. Safety assessments included: vital signs (blood pressure, heart rate, respiration rate and body temperature), ECGs, physical examinations, safety haematology and biochemistry blood tests.
Subjects were excluded at Screening if any of the safety assessments were out of normal range and deemed clinically significant by the Investigator. Stopping criteria were listed in the protocol and included (non-exhaustive) liver chemistry results, an SAE that is considered to be possibly or probably related to the study treatment, an adverse event or protocol deviation occurs that, in the opinion of the investigator, makes it unsafe for the subject to continue in the study.
An Independent Data Monitoring Committee (IDMC) reviewed the unblinded safety data on an approximately quarterly basis. The IDMC also conducted one planned interim analysis once approximately 50% of the study subjects had been enrolled and completed the study up to Day 28. The interim analysis focused on an analysis of the primary efficacy endpoint and an assessment of the safety data. The IDMC could recommend termination or modification of the study based upon a review of the totality of the safety and primary efficacy data.

Background therapy:

N/A

Evidence for comparator:

A placebo comparator was used in this study as there are currently no approved pharmaceutical treatments for tinnitus.
The study was randomised in order to prevent bias in the allocation of treatment and to ensure the comparability of baseline characteristics between the treatment groups. In order to prevent bias in the conduct of the clinical assessments, the study was double blind, so that neither the investigator nor the subject knew whether the subject was receiving active treatment or placebo. Minimisation techniques were employed to balance stratification variables across the two arms.

Actual start date of recruitment	10 November 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 91
Worldwide total number of subjects	91
EEA total number of subjects	91

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)	78
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited at 18 NHS hospitals across England between 10 November 2014 and 08 Oct 2015.

Pre-assignment

Screening details:

A total of 212 subjects provided informed consent and attended for a screening examination. Of these, 91 satisfied inclusion and exclusion criteria and were randomised into the study, the first subject being randomised on 15 Jan 2015; last subject on 07 Oct 2015.

Pre-assignment period milestones

Number of subjects started	212[1]
Number of subjects completed	91

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screen Fail: 121

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects enrolled was considered as the number of subjects dosed on study, e.g. 91 subjects. The number of subjects that were consented and screened was 212, of these 121 subjects failed screening.

Period 1

Period 1 title	Baseline Pre-dose Day 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

A telephone based Interactive Voice Response System (IVRS) was used to allocate subjects to active or placebo treatments

Arms

Are arms mutually exclusive?	Yes
Arm title	AUT00063 800mg

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	AUT00063
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

N/A - Pre-dose

Arm title	Placebo

Arm description: -

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

N/A - Pre-dose

Number of subjects in period 1	AUT00063 800mg	Placebo
Started	44	47
Completed	44	47

Period 2

Period 2 title	Dosing - Day 1 to Day 28
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

A telephone based Interactive Voice Recognition System (IVRS) was used to randomise subjects to either active or placebo arms.

Arms

Are arms mutually exclusive?	Yes
Arm title	AUT00063 800mg

Arm description:

Subjects were required to take 4 x 200mg capsules of AUT00063 to achieve the 800mg dose, once daily after food.

Arm type	Active comparator
Investigational medicinal product name	AUT00063
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects were required to take 4 x 200mg capsules of AUT00063 to achieve the 800mg dose, once daily after food.

Arm title	Placebo

Arm description:

Subjects were required to take 4 capsules once daily after food. Placebo capsules visually match AUT00063 capsules.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects were required to take 4 capsules once daily, after food. Placebo capsules visually match AUT00063 capsules.

Number of subjects in period 2	AUT00063 800mg	Placebo
Started	44	47
Completed	34	39
Not completed	10	8
Consent withdrawn by subject	1	-
Physician decision	1	-
Study closed to recruitment	-	1
Study terminated by Sponsor	6	5
Adverse event, non-fatal	1	1
Lost to follow-up	1	1

Period 3	
Period 3 title	Follow Up - Day 29 to Day 42
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Carer, Subject, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	AUT00063 800mg

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	AUT00063
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

N/A

Arm title	Placebo

Arm description: -

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

N/A

Number of subjects in period 3	AUT00063 800mg	Placebo
Started	34	39
Completed	33	38
Not completed	1	1
Incomplete visit	1	1

Baseline characteristics

Reporting groups	
Reporting group title	AUT00063 800mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	AUT00063 800mg	Placebo	Total
Number of subjects	44	47	91
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	38	40	78
From 65-84 years	6	7	13
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	10	10	20
Male	34	37	71

End points

End points reporting groups

Reporting group title	AUT00063 800mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	AUT00063 800mg
Reporting group description:	
Subjects were required to take 4 x 200mg capsules of AUT00063 to achieve the 800mg dose, once daily after food.	
Reporting group title	Placebo
Reporting group description:	
Subjects were required to take 4 capsules once daily after food. Placebo capsules visually match AUT00063 capsules.	
Reporting group title	AUT00063 800mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Compare the change from baseline (D1 to D28) of the TFI overall score between AUT00063 (800 mg) and placebo

End point title	Compare the change from baseline (D1 to D28) of the TFI overall score between AUT00063 (800 mg) and placebo
End point description:	
TFI = Tinnitus Functional Index	
End point type	Primary
End point timeframe:	
Baseline (pre-dose Day 1) to Day 28	

End point values	AUT00063 800mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	40		
Units: TFI Score change from baseline				
arithmetic mean (standard deviation)	-1.57 (± 15.215)	-5.8 (± 13.861)		

Statistical analyses

Statistical analysis title	Change from baseline in TFI overall score at Day28
Statistical analysis description:	
The changes from baseline in TFI score were analysed by means of an ANCOVA model controlling for the randomised factor age, gender, hearing loss and tinnitus severity and with baseline values of TFI, tinnitus duration and Noise Exposure Questionnaire overall score as covariates.	
Comparison groups	AUT00063 800mg v Placebo

Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.9842
Method	ANCOVA

Notes:

[1] - The primary efficacy variable will be the effect on Tinnitus severity measured as a clinically significant change (which is considered to be reached at a 13-point mean difference – (Meikle et al., 2012) from baseline in TFI overall score between AUT00063 (800 mg) and placebo at Day 28.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 post dose to Follow Up visit(Day 42)

Adverse event reporting additional description:

Adverse events were collected at all study visits, from diary card entries (Day 2 -27) and one phone call on Day 14.
All adverse events (AEs) were recorded in the CRF. AEs were followed-up until the event is resolved or no queries are outstanding when the subject completes the study (End of Study visit).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	AUT00063 800mg
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	AUT00063 800mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 44 (2.27%)	1 / 47 (2.13%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Pyrexia	Additional description: Pyrexia unknown origin		
subjects affected / exposed	0 / 44 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety	Additional description: Anxiety attack		
subjects affected / exposed	1 / 44 (2.27%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	AUT00063 800mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 44 (72.73%)	23 / 47 (48.94%)	
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 44 (29.55%)	9 / 47 (19.15%)	
occurrences (all)	25	14	
Dizziness			
subjects affected / exposed	7 / 44 (15.91%)	0 / 47 (0.00%)	
occurrences (all)	16	0	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	3 / 44 (6.82%)	1 / 47 (2.13%)	
occurrences (all)	3	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 44 (9.09%)	1 / 47 (2.13%)	
occurrences (all)	4	1	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	3 / 44 (6.82%)	1 / 47 (2.13%)	
occurrences (all)	3	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 44 (9.09%)	0 / 47 (0.00%)	
occurrences (all)	4	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 August 2014	Changes requested by the MHRA - Exclusion criteria was amended to include QTc > 450 msec at baseline. - Emergency un-blinding procedure amended to permit rapid un-blinding. - Inclusion criteria amended to ensure that females of child-bearing potential use two methods of contraception during the trial and at least 30 days after the last dose. - Other non-substantial administrative changes
13 November 2014	- Testing conditions (250Hz have been deleted) and limits of the sensorineural hearing loss (Inclusion criteria 4.) have been amended to include: =20dB and =60dB. - Exclusion criterion 18. has been changed to only those surgeries or medical conditions that are expected to significantly affect absorption of medicines. - Prohibited concomitant treatments have been amended to remove exclusion of strenuous exercise from screening until day 42. - Other non-substantial changes for clarification
09 February 2015	- Randomization the minimisation factor "hearing loss" has been amended to include two more pure tone average thresholds at 6 and 8 kHz. - The hearing loss definitions have been amended to mild = ≤40 dB and moderate = ≥41 dB. - Subject Inclusion Criteria the 4th item has been changed to "Sensorineural hearing loss defined by any single audiometric threshold estimate >20 dB for frequencies at 0.5, 1, 2, 4, 6 and 8 kHz, and a Pure Tone Average (of thresholds at, 500, 1000, 2000 and 4000Hz) ≤60dB Hearing Loss (HL)). - The following paragraph has been added to Screening description: Where one or more correctable exclusion criteria are found at screening, after appropriate management the subject can be re-screened. - Interim Analysis and Sample Size Review, the interim analysis has been adapted to be performed when approximately 50% subjects have been enrolled and completed the study up to day 28 which is when the primary efficacy and substantial amount of safety data is available. - Other non-substantial changes
02 July 2015	- Description of Pre-Screening activities '….at the site." was changed to "within and/or between sites' to clarify that the data will be interchanged between the sites. - Other non-substantial changes

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

08 October 2015	Following the planned unblinded interim analysis, which was conducted once around 50% of subjects had completed Day 28, on the 30 Sept 2015, the recommendation of the IDMC was to discontinue the QUIET-1 study based on efficacy data. This recommendation was a consequence of the p-value of the primary analysis exceeding the futility boundary stated in the protocol. No safety issues were identified. On the basis of this recommendation and following an internal review of the data by Autifony, Autifony decided to terminate enrolment into the QUIET-1 study, effective from 08 Oct 2015.	-

Notes:

Limitations and caveats

None reported