Clinical trial results:
A Pilot Double-blind, Placebo-controlled Crossover Study to Explore the Possible Benefit of AUT00063, an Oral Modulator of Voltage-gated Potassium Channels, in Adult Post-lingual Unilateral Cochlear Implant Recipients: The QuicK+fire-study

Summary

EudraCT number	2015-003929-34
Trial protocol	GB
Global end of trial date	10 April 2017

Results information

Result version number	v1 (current)
This version publication date	11 April 2018
First version publication date	11 April 2018

Trial information

Trial identification

Sponsor protocol code	AUT042063

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02832128
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Autifony Therapeutics Limited
Sponsor organisation address	Stevenage Bioscience Catalyst, Stevenage, United Kingdom,
Public contact	Clinical Project Manager, Autifony Therapeutics Limited , info@autifony.com
Scientific contact	Clinical Project Manager, Autifony Therapeutics Limited , +44 203 763 9477, alice.sharman@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	28 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 April 2017
Global end of trial reached?	Yes
Global end of trial date	10 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this pilot study was to explore whether repeat doses of AUT00063 can provide an indication of improvement in performance of tests across a battery of speech and hearing assessments in Cochlear Implant (CI) users. For this purpose, the performance of volunteers who recently received a unilateral CI for post-lingual deafness was assessed by means of speech tests such as the tests comprising the new Minimum Speech Test Battery (MSTB) (Advanced Bionics 2011). The study also explored the effects of repeat doses of AUT00063 on parameters of central auditory processing measured using tests that involve direct stimulation via the CI. In addition, the safety and tolerability of AUT00063 was evaluated in the study subjects.

Fifteen subjects were randomised in a 1:1 ratio to receive either AUT00063 (800 mg/day) or matched placebo for 28 days, followed by a 2- to 4-week washout period before commencing the second 28-day dosing period with the other medication.

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 and Day 28 in both periods and Day 42 (two weeks after last dose). Subjects were also contacted on Day 14 of both periods to collect any adverse events and concomitant medications. Safety assessments included: vital signs (blood pressure, heart rate, and 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 was considered to be possibly or probably related to the study treatment, an adverse event or protocol deviation that occurred that, in the opinion of the investigator, made it unsafe for the subject to continue in the study.

Background therapy:

N/A

Evidence for comparator:

A placebo comparator was used in this study as there are currently no approved pharmaceutical interventions to improve hearing.

Actual start date of recruitment	05 July 2016
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: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

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)	6
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited in the UK (only) between July 2016 and December 2016. Fifteen subjects were enrolled; 8 subjects in the AUT00063 - Placebo group and 7 subjects in the Placebo - AUT00063. All 8 subjects in the AUT00063 - Placebo group completed both periods. Four subjects in the Placebo - AUT00063 group completed and 3 dropped out.

Pre-assignment

Screening details:

A total of 21 subjects attended screening visits. Of these, 15 satisfied satisfied inclusion and exclusion criteria and were randomised into the study, the first subject being screened on 05 July 2016; last subject screened on 15 December 2016.

Pre-assignment period milestones

Number of subjects started	21[1]
Number of subjects completed	15

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screen Fail: 6

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 enrolled is the number of subjects randomised. Six subjects failed screening and are not reported.

Period 1

Period 1 title	Dosing: Day 1 to Day 28 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	AUT00063

Arm description:

AUT00063 800mg

Arm type	Experimental
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: -

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 1	AUT00063	Placebo
Started	14	15
Completed	12	15
Not completed	2	0
Adverse event, non-fatal	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Dosing: Day 1 to Day 28

Reporting group description: -

Reporting group values	Dosing: Day 1 to Day 28	Total	
Number of subjects	15	15	
Age categorical 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)	6	6	
From 65-84 years	9	9	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	66.3		
standard deviation	± 14.55	-	
Gender categorical Units: Subjects			
Female	10	10	
Male	5	5	
Cochlear Implant Device Units: Subjects			
MED-EL	5	5	
Cochlear	9	9	
Advanced Bionics	1	1	
Years since onset of severe/ profound hearing loss Units: Years			
arithmetic mean	22.87		
standard deviation	± 21.797	-	
Years since confirmed qualification for a CI Units: Years			
arithmetic mean	1.64		
standard deviation	± 0.633	-	
Years since CI implantation Units: Years			
arithmetic mean	1.40		
standard deviation	± 0.828	-	

Subject analysis sets	
Subject analysis set title	AUT00063 - Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects were allocated to AUT00063 first and then Placebo in the cross over design	
Subject analysis set title	Placebo - AUT00063
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects were assigned to Placebo first and then AUT00063 in the cross over deisgn	

Reporting group values	AUT00063 - Placebo	Placebo - AUT00063	
Number of subjects	8	7	
Age categorical 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)	1	5	
From 65-84 years	7	2	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	71.8	60.0	
standard deviation	± 6.80	± 18.82	
Gender categorical Units: Subjects			
Female	6	4	
Male	2	3	
Cochlear Implant Device Units: Subjects			
MED-EL	3	2	
Cochlear	5	4	
Advanced Bionics	0	1	
Years since onset of severe/ profound hearing loss Units: Years			
arithmetic mean	20.50	25.57	
standard deviation	± 21.024	± 24.020	
Years since confirmed qualification for a CI Units: Years			
arithmetic mean	1.63	1.67	
standard deviation	± 0.744	± 0.516	
Years since CI implantation Units: Years			
arithmetic mean	1.38	1.43	
standard deviation	± 0.916	± 0.787	

End points

End points reporting groups

Reporting group title	AUT00063
Reporting group description:	
AUT00063 800mg	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	AUT00063 - Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects were allocated to AUT00063 first and then Placebo in the cross over design	
Subject analysis set title	Placebo - AUT00063
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects were assigned to Placebo first and then AUT00063 in the cross over deisgn	

Primary: Consonant-Nucleus-Consonant (CNC) in quiet

End point title	Consonant-Nucleus-Consonant (CNC) in quiet[1]
End point description:	
Consonant-Nucleus-Consonant (CNC) speech test in quiet; Full Analysis Set; Change from Baseline Grand Total in Percent(of total 150 Phonemes).	
End point type	Primary
End point timeframe:	
28 days	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses have been specified due to format.

End point values	AUT00063	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	15		
Units: Mean % Correct				
arithmetic mean (standard deviation)	1.0 (± 8.33)	2.8 (± 8.84)		

Statistical analyses

No statistical analyses for this end point

Primary: AzBio sentences test presented in quiet

End point title	AzBio sentences test presented in quiet[2]
End point description:	
AzBio sentences test presented in quiet; Full Analysis Set; Change from Baseline.	
End point type	Primary

End point timeframe:

28 Days

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses have been specified due to format.

End point values	AUT00063	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	15		
Units: Mean % Correct				
arithmetic mean (standard deviation)	1.3 (± 6.18)	5.1 (± 11.19)		

Statistical analyses

No statistical analyses for this end point

Primary: AzBio sentences test presented in noise

End point title	AzBio sentences test presented in noise[3]

End point description:

AzBio sentences test presented in noise;
Full Analysis Set;
Change from Baseline.

End point type	Primary

End point timeframe:

28 Days

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses have been specified due to format.

End point values	AUT00063	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	15		
Units: Mean % Correct				
arithmetic mean (standard deviation)	0.0 (± 10.31)	-2.7 (± 9.57)		

Statistical analyses

No statistical analyses for this end point

Primary: BKB-SIN test

End point title	BKB-SIN test[4]

End point description:

Bamford-Kowal-Bench Speech-in-Noise [BKB-SIN] sentence test;
Full Analysis Set;
Change from Baseline.
SNR = signal-to-noise ratio

SNR - 50 = 50% correct on BKB-SIN Test

End point type	Primary

End point timeframe:

28 Days

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses have been specified due to format.

End point values	AUT00063	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	15		
Units: Mean Decibels (SNR-50)				
arithmetic mean (standard deviation)	-1.7 (± 3.46)	-1.2 (± 2.71)		

Statistical analyses

No statistical analyses for this end point

Primary: Rate discrimination at low rates

End point title	Rate discrimination at low rates[5]

End point description:

Rate discrimination at low rates (centered on 120 PPS): ANOVA of mean over runs.
Full Analysis Set.

End point type	Primary

End point timeframe:

28 Days

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses have been specified due to format.

End point values	AUT00063	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	15		
Units: Pulses Per Second (PPS)				
geometric mean (confidence interval 95%)	1.211 (1.167 to 1.258)	1.199 (1.166 to 1.233)		

Statistical analyses

No statistical analyses for this end point

Primary: Midpoint comparison for upper limit of rate discrimination

End point title	Midpoint comparison for upper limit of rate discrimination[6]

End point description:

Midpoint comparison for upper limit of rate discrimination (10 trials): ANOVA of upper limit (pps).
Full Analysis Set.

End point type	Primary

End point timeframe:

28 Days

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses have been specified due to format.

End point values	AUT00063	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	15		
Units: Pulses Per Second (PPS)				
geometric mean (confidence interval 95%)	457.178 (349.216 to 598.517)	490.906 (401.604 to 600.065)		

Statistical analyses

No statistical analyses for this end point

Primary: Gap detection

End point title	Gap detection[7]

End point description:

Gap detection (1055 PPS): ANOVA of mean over runs.
Full Analysis Set.

End point type	Primary

End point timeframe:

28 Days

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses have been specified due to format.

End point values	AUT00063	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	15		
Units: milliseconds				
geometric mean (confidence interval 95%)	2.933 (2.562 to 3.359)	2.964 (2.680 to 3.279)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From Day 1 dosing to Follow Up visit (Day 42, two weeks post last dose).	
Adverse event reporting additional description: Treatment Emergent Adverse Events reported.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	AUT00063 800mg
Reporting group description: Treatment-emergent AEs	
Reporting group title	Placebo
Reporting group description: Treatment-emergent AEs reported	

Serious adverse events	AUT00063 800mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	2 / 15 (13.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	AUT00063 800mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 13 (46.15%)	9 / 15 (60.00%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 13 (23.08%)	1 / 15 (6.67%)	
occurrences (all)	4	1	
Headache			
subjects affected / exposed	2 / 13 (15.38%)	2 / 15 (13.33%)	
occurrences (all)	4	2	
Balance			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Influenza like illness			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	2 / 13 (15.38%)	2 / 15 (13.33%)	
occurrences (all)	3	2	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 13 (7.69%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Diarrhoea			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Dry mouth			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Joint swelling			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	1 / 13 (7.69%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
Escherichia infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Oral herpes			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 August 2016	Reduction of the sample size from 20 subjects to 12 subjects; the sample size was calculated to detect a 25% decrease in gap detection which is judged to provide evidence of a meaningful treatment effect, based on unpublished direct stimulation data from the MRC Brain and Cognition Unit that became available after the study start.
22 September 2016	A change to the inclusion criteria relating to the speech test score and time post implant to aid recruitment. Criteria "Less than optimal speech perception at the time of enrolment (defined as a score of 25% to 85% for Bamford-Kowal-Bench (BKB) sentences presented in quiet without contralateral hearing aid)", changed to a score of 25% to 95% BKB sentence test. Criteria "Received a unilateral cochlear implant within the last 9 to 36 months for post-lingual deafness", changed to within the last 9 to 48 months.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported