



Clinical trial results:

A PHASE II RANDOMIZED AND CONTROLLED INVESTIGATION OF SIX WEEKS OF ORAL VALGANCICLOVIR THERAPY IN INFANTS AND CHILDREN WITH CONGENITAL CYTOMEGALOVIRUS INFECTION AND HEARING LOSS.

Summary

EudraCT number	2014-001920-31
Trial protocol	GB
Global end of trial date	03 January 2020

Results information

Result version number	v1 (current)
This version publication date	21 December 2022
First version publication date	21 December 2022
Summary attachment (see zip file)	Summary report (HHSN272201100035C Annual Report 15 Oct 2019.pdf)

Trial information

Trial identification

Sponsor protocol code	DMID11-0069
-----------------------	-------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01649869
WHO universal trial number (UTN)	-
Other trial identifiers	The UK Sponsor is: UCL: 08-0172

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Gower Street, London, United Kingdom,
Public contact	Prof Paul Griffiths, University College London, p.griffiths@ucl.ac.uk
Scientific contact	Prof Paul Griffiths, University College London, p.griffiths@ucl.ac.uk

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	15 August 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 January 2020
Global end of trial reached?	Yes
Global end of trial date	03 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to assess whether a six week course of oral valganciclovir can stabilize the hearing of children with congenital CMV infection who present with hearing loss. This will be accomplished by evaluating changes in hearing in either ear at 6 months from baseline.

Protection of trial subjects:

N/A

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 September 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: 24
Country: Number of subjects enrolled	United States: 11
Worldwide total number of subjects	35
EEA total number of subjects	0

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)	24
Children (2-11 years)	11
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

For this study, subjects were enrolled once they signed the informed consent form (ICF). It was not until after hearing loss was confirmed by audiology testing and confirmation of congenital CMV by dried blood spot that a subject was randomized and started on study drug. This reduced protocol enrolment from 54 to 35.

Pre-assignment

Screening details:

Hearing loss was confirmed by audiology testing and congenital CMV was confirmed by dried blood spot.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

27 Children between 1 month and 3 years of age (up to 4th birthday) with sensorineural hearing loss and documented CMV infection will receive placebo orally twice a day for 6 weeks

Placebo: Simple Syrup as 60-90% sucrose in purified water: given orally twice a day for 6 weeks

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral solution
Routes of administration	Oral use

Dosage and administration details:

Simple Syrup as 60-90% sucrose in purified water: given orally twice a day for 6 weeks.

Arm title	Active
------------------	--------

Arm description:

27 Children between 1 month and 3 years of age (up to 4th birthday) with sensorineural hearing loss and documented CMV infection will receive valganciclovir HCl 16.0 mg/kg orally twice a day for 6 weeks

Valganciclovir: Valcyte (valganciclovir hydrochloride) 50 mg of valganciclovir free base per 1 mL, oral solution: given at 16.0 mg/kg, twice a day for 6 weeks.

Arm type	Experimental
Investigational medicinal product name	Valganciclovir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral solution
Routes of administration	Oral use

Dosage and administration details:

Valcyte (valganciclovir hydrochloride) 50 mg of valganciclovir free base per 1 mL, oral solution: given at 16.0 mg/kg, twice a day for 6 weeks

Number of subjects in period 1	Placebo	Active
Started	18	17
Completed	16	16
Not completed	2	1
Required treatment outside protocol	1	-
Family member illness	1	-
Severe hearing loss borderline eligible	-	1

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
27 Children between 1 month and 3 years of age (up to 4th birthday) with sensoneural hearing loss and documented CMV infection will receive placebo orally twice a day for 6 weeks	
Placebo: Simple Syrup as 60-90% sucrose in purified water: given orally twice a day for 6 weeks	
Reporting group title	Active
Reporting group description:	
27 Children between 1 month and 3 years of age (up to 4th birthday) with sensoneural hearing loss and documented CMV infection will receive valganciclovir HCl 16.0 mg/kg orally twice a day for 6 weeks	
Valganciclovir: Valcyte (valganciclovir hydrochloride) 50 mg of valganciclovir free base per 1 mL, oral solution: given at 16.0 mg/kg, twice a day for 6 weeks.	

Reporting group values	Placebo	Active	Total
Number of subjects	18	17	35
Age categorical			
27 Children between 1 month and 3 years of age (up to 4th birthday) with sensoneural hearing loss and documented CMV infection will receive placebo orally twice a day for 6 weeks			
Placebo: Simple Syrup as 60-90% sucrose in purified water: given orally twice a day for 6 weeks			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: months			
median	19.5	17.8	
standard deviation	± 13.1	± 5.8	-
Gender categorical			
Units: Subjects			
Female	8	6	14
Male	10	11	21

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: 27 Children between 1 month and 3 years of age (up to 4th birthday) with sensorineural hearing loss and documented CMV infection will receive placebo orally twice a day for 6 weeks	
Placebo: Simple Syrup as 60-90% sucrose in purified water: given orally twice a day for 6 weeks	
Reporting group title	Active
Reporting group description: 27 Children between 1 month and 3 years of age (up to 4th birthday) with sensorineural hearing loss and documented CMV infection will receive valganciclovir HCl 16.0 mg/kg orally twice a day for 6 weeks	
Valganciclovir: Valcyte (valganciclovir hydrochloride) 50 mg of valganciclovir free base per 1 mL, oral solution: given at 16.0 mg/kg, twice a day for 6 weeks.	
Subject analysis set title	Randomized
Subject analysis set type	Sub-group analysis
Subject analysis set description: Randomized children between 1 month and 3 years of age (up to 4th birthday) with sensorineural hearing loss and documented CMV infection will receive placebo orally twice a day for 6 weeks	

Primary: Number of Ears That Had (1) Improved Hearing or no Change in Hearing (2) Worsened Hearing.

End point title	Number of Ears That Had (1) Improved Hearing or no Change in Hearing (2) Worsened Hearing.
End point description: A single, independent study audiologist who is masked (blinded) to treatment assignment will assess the audiology test battery for each subject and assign the classifications of normal hearing, mild hearing loss, moderate hearing loss, or severe hearing loss based upon their hearing thresholds (in decibels). The classifications will be assigned by ear (one for the left ear and one for the right ear), giving "total ear" classifications. At the analyses stage, the "best ear" classification for the subject at that study visit will be determined; for example, if a subject had mild hearing loss in their left ear and severe hearing loss in their right ear, then the "best ear" classification will be mild hearing loss. Not both ears are evaluable for all subjects. In some subjects, only one ear is evaluable.	
End point type	Primary
End point timeframe: Day 1 through Day 180	

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	15		
Units: Ears				
Improve + no change	27	20		
Worsened	1	6		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Active
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0859
Method	Generalized linear model for binary outc

Secondary: Number of Best Ear That Had (1) Improved Hearing or no Change in Hearing (2) Worsened Hearing [ex. Improved+ no Change (Normal to Normal) Versus Other].

End point title	Number of Best Ear That Had (1) Improved Hearing or no Change in Hearing (2) Worsened Hearing [ex. Improved+ no Change (Normal to Normal) Versus Other].
-----------------	--

End point description:

A single, independent study audiologist who is masked (blinded) to treatment assignment will assess the audiology test battery for each subject and assign the classifications of normal hearing, mild hearing loss, moderate hearing loss, or severe hearing loss based upon their hearing thresholds (in decibels). The classifications will be assigned by ear (one for the left ear and one for the right ear), giving "total ear" classifications. At the analyses stage, the "best ear" classification for the subject at that study visit will be determined; for example, if a subject had mild hearing loss in their left ear and severe hearing loss in their right ear, then the "best ear" classification will be mild hearing loss. For this outcome, we combine the improved hearing and no change for the special case only of normal to normal. Other category include worsened and no change from (1) mild to mild hearing loss, (2) moderate to moderate hearing loss, or (3) severe to severe hearing loss.

End point type	Secondary
----------------	-----------

End point timeframe:

Day 1 through Day 180

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	12		
Units: Participants				
Improved + normal to normal	9	6		
No change abnormal or worsened	6	6		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Active
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7068
Method	Fisher exact

Secondary: Adverse Event (AE) Resulting in Unanticipated Medically Attended Visit

End point title	Adverse Event (AE) Resulting in Unanticipated Medically Attended Visit
-----------------	--

End point description:

Adverse event resulting in unanticipated medically attended visit. This outcome summarizes the number of adverse events (AEs) that resulted in the unanticipated medically attended visit.

End point type	Secondary
----------------	-----------

End point timeframe:

Day 1 thru day 70

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: Participants				
No	15	17		
Yes	3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse Event (AE) Resulting in Unresolved Outcome

End point title	Adverse Event (AE) Resulting in Unresolved Outcome
-----------------	--

End point description:

Adverse event resulting in unresolved outcome. This outcome summarizes the number of adverse events (AEs) that resulted in unresolved outcome of that AE.

End point type	Secondary
----------------	-----------

End point timeframe:

Day 1 thru day 70

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	17		
Units: Participants				
No	18	17		
Yes	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Adverse Events in the Active Group That Resulted in Discontinuation of Valganciclovir

End point title	Number of Adverse Events in the Active Group That Resulted in Discontinuation of Valganciclovir ^[1]
-----------------	--

End point description:

AE resulting in discontinuation of valganciclovir (active group only). This outcome summarizes the number of adverse events (AEs) that resulted in the discontinuation of valganciclovir in the active group only.

End point type	Secondary
----------------	-----------

End point timeframe:

Day 1 thru day 70

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was just for the participants who had randomised to receive the IMP.

End point values	Active			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: Participants				
No	17			
Yes	0			

Statistical analyses

No statistical analyses for this end point

Secondary: The Quantitative Log Reduction in CMV in Saliva Detected After 6 Weeks of Therapy

End point title	The Quantitative Log Reduction in CMV in Saliva Detected After 6 Weeks of Therapy
-----------------	---

End point description:

The quantitative log reduction in CMV in saliva (urine) detected after 6 weeks of therapy. Quantitative viral load by PCR in log 10 units measured in urine after 6 weeks of therapy; if undetectable, viral load is assigned a value of 10 (1 in log 10 units)

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline thru months 6

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	17		
Units: log10 IU/ml				
least squares mean (confidence interval 95%)	0.0057 (-0.6395 to 0.6508)	1.3202 (0.6894 to 1.9509)		

Statistical analyses

No statistical analyses for this end point

Secondary: The Quantitative Log Reduction in Viruria Detected After 6 Weeks of Therapy

End point title	The Quantitative Log Reduction in Viruria Detected After 6 Weeks of Therapy
End point description:	
The quantitative log reduction in viruria (urine) detected after 6 weeks of therapy. Quantitative viral load by PCR in log 10 units measured in urine after 6 weeks of therapy; if undetectable, viral load is assigned a value of 10 (1 in log 10 units)	
End point type	Secondary
End point timeframe:	
Baseline thru months 6	

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	15		
Units: log10 IU/ml				
least squares mean (confidence interval 95%)	0.8390 (-0.05057 to 1.7286)	1.2152 (0.5274 to 1.9029)		

Statistical analyses

No statistical analyses for this end point

Secondary: The Quantitative Log Change in Viremia From Baseline to Month 6.

End point title	The Quantitative Log Change in Viremia From Baseline to Month 6.
End point description:	
The quantitative change (Month 6 minus baseline) in viremia (blood) Quantitative viral load by PCR in log 10 units measured in urine after 6 weeks of therapy; if undetectable, viral load is assigned a value of 10 (1 in log 10 units).	
End point type	Secondary
End point timeframe:	
Baseline to month 6	

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	17		
Units: log10 IU/ml				
least squares mean (confidence interval 95%)	-0.1528 (-0.5721 to 0.2664)	0.4908 (0.08108 to 0.9005)		

Statistical analyses

No statistical analyses for this end point

Secondary: Detection of CMV in Saliva PCR Six Month After Trial Entry

End point title	Detection of CMV in Saliva PCR Six Month After Trial Entry
End point description:	Each subject either has positive or negative PCR results. Virus is detected if the PCR is positive.
End point type	Secondary
End point timeframe:	At 6 months

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: Participants				
Positive	8	7		
Negative	8	9		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Active
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

Secondary: Detection of CMV in Saliva by PCR Six Weeks After Trial Entry

End point title	Detection of CMV in Saliva by PCR Six Weeks After Trial Entry
-----------------	---

End point description:

Each subject either has positive or negative PCR results. Virus is detected if the PCR is positive.

End point type	Secondary
----------------	-----------

End point timeframe:

At 6 weeks (Day 42)

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: Participants				
Positive	9	3		
Negative	7	13		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Active v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0659
Method	Fisher exact

Secondary: Detection of Viremia (Blood) by PCR Six Month After Trial Entry

End point title	Detection of Viremia (Blood) by PCR Six Month After Trial Entry
-----------------	---

End point description:

Each subject either has positive or negative PCR results. Virus is detected if the PCR is positive.

End point type	Secondary
----------------	-----------

End point timeframe:

At 6 months

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: Participants				
Positive	4	3		
Negative	11	12		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Active
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

Secondary: Detection of Viremia (Blood) by PCR Six Weeks After Trial Entry

End point title	Detection of Viremia (Blood) by PCR Six Weeks After Trial Entry
End point description:	Each subject either has positive or negative PCR results. Virus is detected if the PCR is positive.
End point type	Secondary
End point timeframe:	At 6 weeks (Day 42)

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	14		
Units: Participants				
Positive	4	2		
Negative	11	12		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Active
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6513
Method	Fisher exact

Secondary: Detection of Viruria (Urine) by PCR Six Month After Trial Entry

End point title	Detection of Viruria (Urine) by PCR Six Month After Trial Entry
-----------------	---

End point description:

Each subject either has positive or negative PCR results. Virus is detected if the PCR is positive.

End point type	Secondary
----------------	-----------

End point timeframe:

At 6 months

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	14		
Units: Participants				
Positive	10	11		
Negative	1	3		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Active
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6043
Method	Fisher exact

Secondary: Detection of Viruria (Urine) by PCR Six Weeks After Trial Entry

End point title	Detection of Viruria (Urine) by PCR Six Weeks After Trial Entry
-----------------	---

End point description:

Each subject either has positive or negative PCR results. Virus is detected if the PCR is positive.

End point type	Secondary
----------------	-----------

End point timeframe:

At 6 weeks (Day 42)

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: Participants				
Positive	11	1		
Negative	1	11		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Active
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Fisher exact

Secondary: Change in Total Ear Hearing Assessments [Worse Versus Other] Between Baseline and Study Month 6.

End point title	Change in Total Ear Hearing Assessments [Worse Versus Other] Between Baseline and Study Month 6.
-----------------	--

End point description:

A single, independent study audiologist who is masked (blinded) to treatment assignment will assess the audiology test battery for each subject and assign the classifications of normal hearing, mild hearing loss, moderate hearing loss, or severe hearing loss based upon their hearing thresholds (in decibels). The classifications will be assigned by ear (one for the left ear and one for the right ear), giving "total ear" classifications. At the analyses stage, the "best ear" classification for the subject at that study visit will be determined; for example, if a subject had mild hearing loss in their left ear and severe hearing loss in their right ear, then the "best ear" classification will be mild hearing loss.

End point type	Secondary
----------------	-----------

End point timeframe:

Day 1 through Day 180

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	15		
Units: Ears				
Worsened	1	6		
Other	27	20		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Active

Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0859
Method	Generalized linear model for binary outc

Secondary: Change in Total Ear Hearing Assessments [Worse+ no Change (Abnormal to Abnormal) Versus Other] Between Baseline and Study Month 6.

End point title	Change in Total Ear Hearing Assessments [Worse+ no Change (Abnormal to Abnormal) Versus Other] Between Baseline and Study Month 6.
-----------------	--

End point description:

A single, independent study audiologist who is masked (blinded) to treatment assignment will assess the audiology test battery for each subject and assign the classifications of normal hearing, mild hearing loss, moderate hearing loss, or severe hearing loss based upon their hearing thresholds (in decibels). The classifications will be assigned by ear (one for the left ear and one for the right ear), giving "total ear" classifications. At the analyses stage, the "best ear" classification for the subject at that study visit will be determined; for example, if a subject had mild hearing loss in their left ear and severe hearing loss in their right ear, then the "best ear" classification will be mild hearing loss.

End point type	Secondary
----------------	-----------

End point timeframe:

Day 1 through Day 180

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	15		
Units: Ears				
worse + no change (abnormal to abnormal)	19	20		
Other	9	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Total Ear Hearing Assessments [Improved Versus Other] Between Baseline and Study Month 6.

End point title	Change in Total Ear Hearing Assessments [Improved Versus Other] Between Baseline and Study Month 6.
-----------------	---

End point description:

A single, independent study audiologist who is masked (blinded) to treatment assignment will assess the audiology test battery for each subject and assign the classifications of normal hearing, mild hearing loss, moderate hearing loss, or severe hearing loss based upon their hearing thresholds (in decibels). The classifications will be assigned by ear (one for the left ear and one for the right ear), giving "total ear" classifications. At the analyses stage, the "best ear" classification for the subject at that study visit will be determined; for example, if a subject had mild hearing loss in their left ear and severe hearing loss in their right ear, then the "best ear" classification will be mild hearing loss.

End point type	Secondary
----------------	-----------

End point timeframe:
Day 1 through Day 180

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	15		
Units: Ears				
Improved	0	0		
Other	28	26		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Best Ear Hearing Assessments [Worse Versus Other] Between Baseline and Study Month 6.

End point title	Change in Best Ear Hearing Assessments [Worse Versus Other] Between Baseline and Study Month 6.
-----------------	---

End point description:

A single, independent study audiologist who is masked (blinded) to treatment assignment will assess the audiology test battery for each subject and assign the classifications of normal hearing, mild hearing loss, moderate hearing loss, or severe hearing loss based upon their hearing thresholds (in decibels). The classifications will be assigned by ear (one for the left ear and one for the right ear), giving "total ear" classifications. At the analyses stage, the "best ear" classification for the subject at that study visit will be determined; for example, if a subject had mild hearing loss in their left ear and severe hearing loss in their right ear, then the "best ear" classification will be mild hearing loss.

End point type	Secondary
----------------	-----------

End point timeframe:
Day 1 through Day 180

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	12		
Units: Participants				
Worsened	0	3		
Other	15	9		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Active

Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0752
Method	Fisher exact

Secondary: Change in Best Ear Hearing Assessments [Worse + no Change (Abnormal to Abnormal) Versus Other] Between Baseline and Study Month 6.

End point title	Change in Best Ear Hearing Assessments [Worse + no Change (Abnormal to Abnormal) Versus Other] Between Baseline and Study Month 6.
-----------------	--

End point description:

A single, independent study audiologist who is masked (blinded) to treatment assignment will assess the audiology test battery for each subject and assign the classifications of normal hearing, mild hearing loss, moderate hearing loss, or severe hearing loss based upon their hearing thresholds (in decibels). The classifications will be assigned by ear (one for the left ear and one for the right ear), giving "total ear" classifications. At the analyses stage, the "best ear" classification for the subject at that study visit will be determined; for example, if a subject had mild hearing loss in their left ear and severe hearing loss in their right ear, then the "best ear" classification will be mild hearing loss.

End point type	Secondary
----------------	-----------

End point timeframe:

Day 1 through Day 180

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	12		
Units: Participants				
No change abnormal to abnormal + worsened	6	6		
Improved + normal to normal	9	6		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Active v Placebo
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7068
Method	Fisher exact

Secondary: Change in Best Ear Hearing Assessments [Improved Versus Other] Between Baseline and Study Month 6.

End point title	Change in Best Ear Hearing Assessments [Improved Versus
-----------------	---

End point description:

A single, independent study audiologist who is masked (blinded) to treatment assignment will assess the audiology test battery for each subject and assign the classifications of normal hearing, mild hearing loss, moderate hearing loss, or severe hearing loss based upon their hearing thresholds (in decibels). The classifications will be assigned by ear (one for the left ear and one for the right ear), giving "total ear" classifications. At the analyses stage, the "best ear" classification for the subject at that study visit will be determined; for example, if a subject had mild hearing loss in their left ear and severe hearing loss in their right ear, then the "best ear" classification will be mild hearing loss.

End point type	Secondary
----------------	-----------

End point timeframe:

Day 1 through Day 180

End point values	Placebo	Active		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	12		
Units: Participants				
Improved	0	0		
No change or worsened	15	12		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Active
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

Secondary: Association of Change in Viral Load (Blood) With Change in Total Ear Hearing at 6 Months

End point title	Association of Change in Viral Load (Blood) With Change in Total Ear Hearing at 6 Months
-----------------	--

End point description:

Analysis of actual viral load was done using log base 10 transformation. Undetectable viral load value was replaced by a value of 10. A summary measure of the viral load over time considers all time points available by calculating the average area under the curve (AUC) (trapezoidal rule) applied to the log base 10 viral load. Average is based on the maximum period of time with viral load data for a given subject. The average or standardize AUC units is therefore the original AUC units of log 10 copies/ml*days divided by days in study which equals log 10 copies/ml.

End point type	Secondary
----------------	-----------

End point timeframe:

At 6 months

End point values	Randomized			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: Ears				
log mean (standard deviation)				
Improved + normal to normal	1.396 ($\pm$ 0.542)			
No change abnormal + worsened	1.326 ($\pm$ 0.566)			

Statistical analyses

No statistical analyses for this end point

Secondary: Association of Change in Viral Load (Saliva) With Change in Total Ear Hearing at 6 Months

End point title	Association of Change in Viral Load (Saliva) With Change in Total Ear Hearing at 6 Months
-----------------	---

End point description:

Analysis of actual viral load was done using log base 10 transformation. Undetectable viral load value was replaced by a value of 10. A summary measure of the viral load over time considers all time points available by calculating the average area under the curve (AUC) (trapezoidal rule) applied to the log base 10 viral load. Average is based on the maximum period of time with viral load data for a given subject. The average or standardize AUC units is therefore the original AUC units or log 10 copies/ml*days divided by days in study which equals log 10 copies/ml.

End point type	Secondary
----------------	-----------

End point timeframe:

At 6 months

End point values	Randomized			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: log 10 copies/ml				
log mean (standard deviation)				
Improved + normal to normal	2.447 ($\pm$ 1.715)			
No change abnormal + worsened	2.290 ($\pm$ 1.349)			

Statistical analyses

No statistical analyses for this end point

Secondary: Association of Change in Viral Load (Urine) With Change in Total Ear Hearing at 6 Months

End point title	Association of Change in Viral Load (Urine) With Change in Total Ear Hearing at 6 Months
-----------------	--

End point description:

Analysis of actual viral load was done using log base 10 transformation. Undetectable viral load value was replaced by a value of 10. A summary measure of the viral load over time considers all time points available by calculating the average area under the curve (AUC) (trapezoidal rule) applied to the log base 10 viral load. Average is based on the maximum period of time with viral load data for a given subject. The average or standardize AUC units is therefore the original AUC units of log 10 copies/ml*days divided by days in study which equals log 10 copies/ml.

End point type	Secondary
----------------	-----------

End point timeframe:

At 6 months

End point values	Randomized			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: log 10 copies/ml				
log mean (standard deviation)				
Improved + normal to normal	3.562 (± 1.139)			
No change abnormal + worsened	3.583 (± 1.370)			

Statistical analyses

No statistical analyses for this end point

Secondary: Association of Change in Viral Load (Blood) With Change in Best Ear Hearing at 6 Months

End point title	Association of Change in Viral Load (Blood) With Change in Best Ear Hearing at 6 Months
-----------------	---

End point description:

Analysis of actual viral load was done using log base 10 transformation. Undetectable viral load value was replaced by a value of 10. A summary measure of the viral load over time considers all time points available by calculating the average area under the curve (AUC) (trapezoidal rule) applied to the log base 10 viral load. Average is based on the maximum period of time with viral load data for a given subject. The average or standardize AUC units is therefore the original AUC units of log 10 copies/ml*days divided by days in study which equals log 10 copies/ml.

End point type	Secondary
----------------	-----------

End point timeframe:

At 6 months

End point values	Randomized			
Subject group type	Subject analysis set			
Number of subjects analysed	27			
Units: log 10 copies/ml				
log mean (standard deviation)				
Improved + normal to normal	1.396 (± 0.542)			
No change abnormal + worsened	1.359 (± 0.668)			

Statistical analyses

No statistical analyses for this end point

Secondary: Association of Change in Viral Load (Saliva) With Change in Best Ear Hearing at 6 Months

End point title	Association of Change in Viral Load (Saliva) With Change in Best Ear Hearing at 6 Months
-----------------	--

End point description:

Analysis of actual viral load was done using log base 10 transformation. Undetectable viral load value was replaced by a value of 10. A summary measure of the viral load over time considers all time points available by calculating the average area under the curve (AUC) (trapezoidal rule) applied to the log base 10 viral load. Average is based on the maximum period of time with viral load data for a given subject. The average or standardize AUC units is therefore the original AUC units of log 10 copies/ml*days divided by days in study which equals log 10 copies/ml.

End point type	Secondary
----------------	-----------

End point timeframe:

At 6 months

End point values	Randomized			
Subject group type	Subject analysis set			
Number of subjects analysed	27			
Units: log 10 copies/ml				
log mean (standard deviation)				
Improved + normal to normal	2.447 (± 1.715)			
No change abnormal + worsened	2.423 (± 1.484)			

Statistical analyses

No statistical analyses for this end point

Secondary: Association of Change in Viral Load (Urine) With Change in Best Ear Hearing at 6 Months

End point title	Association of Change in Viral Load (Urine) With Change in Best Ear Hearing at 6 Months
-----------------	---

End point description:

Analysis of actual viral load was done using log base 10 transformation. Undetectable viral load value was replaced by a value of 10. A summary measure of the viral load over time considers all time points available by calculating the average area under the curve (AUC) (trapezoidal rule) applied to the log base 10 viral load. Average is based on the maximum period of time with viral load data for a given subject. The average or standardize AUC units is therefore the original AUC units of log 10 copies/ml*days divided by days in study which equals log 10 copies/ml.

End point type	Secondary
----------------	-----------

End point timeframe:

At 6 months

End point values	Randomized			
Subject group type	Subject analysis set			
Number of subjects analysed	25			
Units: log 10 copies/ml				
log mean (standard deviation)				
Improved + normal to normal	3.562 (± 1.139)			
No change abnormal + worsened	3.831 (± 1.570)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were recorded from Study Day 1 until 4 weeks after last dose of study drug.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	25.1
--------------------	------

Reporting groups

Reporting group title	Active Group
-----------------------	--------------

Reporting group description:

Participants received study drug.

Reporting group title	Placebo Group
-----------------------	---------------

Reporting group description:

Participants received placebo.

Serious adverse events	Active Group	Placebo Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Respiratory distress			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (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	Active Group	Placebo Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 17 (76.47%)	12 / 18 (66.67%)	
General disorders and administration site conditions			
Hypermetropia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Pyrexia			

subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2	4 / 18 (22.22%) 4	
Condition aggravated subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Epistaxis subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 18 (5.56%) 1	
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2	2 / 18 (11.11%) 6	
Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Bronchiolitis subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2	0 / 18 (0.00%) 0	
Nasal congestion subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Respiratory tract infection subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Rhinitis subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 2	2 / 18 (11.11%) 3	
Rhinovirus infection subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Asthma subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Psychiatric disorders			

Screaming subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Lethargy subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Hallucination subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Agitation subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 18 (5.56%) 1	
Psychomotor hyperactivity subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 18 (5.56%) 1	
Crying subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	2 / 18 (11.11%) 2	
Investigations Blood urine present subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Protein urine present subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Haemoglobin decreased subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 18 (5.56%) 1	
Injury, poisoning and procedural complications Injury subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2	0 / 18 (0.00%) 0	
Fracture subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Limb injury			

subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Fall subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 18 (5.56%) 1	
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	2 / 18 (11.11%) 4	
Monocytopenia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Ear and labyrinth disorders Ear infection subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2	1 / 18 (5.56%) 1	
Auditory disorder subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 3	0 / 18 (0.00%) 0	
Otitis media subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 18 (5.56%) 1	
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	2 / 18 (11.11%) 3	
Vomiting subjects affected / exposed occurrences (all)	5 / 17 (29.41%) 5	2 / 18 (11.11%) 5	
Decreased appetite subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Weight decreased subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Gastroenteritis viral			

subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Teething			
subjects affected / exposed	2 / 17 (11.76%)	2 / 18 (11.11%)	
occurrences (all)	2	2	
Diarrhoea			
subjects affected / exposed	1 / 17 (5.88%)	1 / 18 (5.56%)	
occurrences (all)	1	2	
Gastroenteritis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Reflux gastritis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Petechiae			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Dermatitis diaper			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Rash erythematous			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Impetigo			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Rash papular			
subjects affected / exposed	1 / 17 (5.88%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Pallor			
subjects affected / exposed	0 / 17 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	

Renal and urinary disorders Urinary incontinence subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 18 (5.56%) 1	
Musculoskeletal and connective tissue disorders Osteopenia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	
Infections and infestations Viral infection subjects affected / exposed occurrences (all) Hand-foot-and-mouth disease subjects affected / exposed occurrences (all) Tonsillitis subjects affected / exposed occurrences (all) Postoperative wound infection subjects affected / exposed occurrences (all) Varicella subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1 1 / 17 (5.88%) 1 1 / 17 (5.88%) 1 1 / 17 (5.88%) 1 0 / 17 (0.00%) 0 0 / 17 (0.00%) 0	2 / 18 (11.11%) 3 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1 0 / 18 (0.00%) 0 1 / 18 (5.56%) 1 2 / 18 (11.11%) 2	
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 18 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported