Clinical trial results:
Efficacy of AM-111 in Patients with Acute Sensorineural Hearing Loss: A Multi-Centre, Double-Blind, Randomised, Placebo-Controlled, Dose-Escalation Phase II Study

Summary

EudraCT number	2008-000132-40
Trial protocol	DE CZ
Global end of trial date	17 July 2012

Results information

Result version number	v1 (current)
This version publication date	06 August 2016
First version publication date	06 August 2016

Trial information

Trial identification

Sponsor protocol code	AM-111-CL-08-01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Auris Medical AG
Sponsor organisation address	Falknerstr. 4, Basel, Switzerland, 4001
Public contact	Thomas Meyer, Auris Medical AG, +41 61 201 13 50, ear@aurismedical.com
Scientific contact	Thomas Meyer, Auris Medical AG, +41 61 201 13 50, ear@aurismedical.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	18 June 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 July 2012
Global end of trial reached?	Yes
Global end of trial date	17 July 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was the evaluation of the therapeutic benefit of a single intratympanic (i.t.) AM-111 injection in comparison to placebo in the treatment of acute sensorineural hearing loss (ASNHL).

Protection of trial subjects:

This Clinical Trial was conducted in accordance with the study protocol, the International Conference on Harmonisation (ICH) harmonized tripartite guideline on Good Clinical Practices (GCP) (E6), as well as the ethical principles outlined in the Declaration of Helsinki dated 1989, respectively in their most current version.

Background therapy:

Reserve therapy option: Subjects whose pure tone average (PTA) recovered on average less than 10 dB from baseline to Day7 were given the option to receive a 5-day course of prednisolone by way of oral administration (2 x 50 mg daily).

Evidence for comparator: -

Actual start date of recruitment	05 February 2009
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	Germany: 41
Country: Number of subjects enrolled	Poland: 143
Country: Number of subjects enrolled	Czech Republic: 26
Worldwide total number of subjects	210
EEA total number of subjects	210

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)	210
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Twenty-five European sites (academic tertiary referral centers and private ENT practices) from 3 EU countries participated in the study. A total of 210 patients were screened. Of these, all 210 patients were randomised.

Pre-assignment

Screening details:

Main inclusion criteria were: Age 18 - 60 years; unilateral ISSNHL or uni-or bilateral AAT; hearing loss at least 30 dB; onset not more than 48h before.
All 210 screened patients have been randomised.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	AM-111 0.4 mg/mL

Arm description:

Study drug (gel formulation) was administered on Day 0 by intratympanic injection under local anesthesia of the tympanic membrane.
Patients came back for 3 further follow-up visits on Days 3, 7, 30, and 90.
Glass vials containing 0.7 mL of the gel formulation were provided for each treatment visit of which 0.25 mL were used for treatment.

Arm type	Experimental
Investigational medicinal product name	JNK inhibitor (D-JNKI-1)
Investigational medicinal product code	AM-111
Other name	
Pharmaceutical forms	Gel for injection
Routes of administration	Intratympanic use

Dosage and administration details:

Single intratympanic application of AM-111 0.4 mg/mL (0.25 mL). In case of bilateral AAT, only the worse affected ear was treated.

Arm title	AM-111 2.0 mg/mL

Arm description:

Study drug (gel formulation) was administered on Day 0 by intratympanic injection under local anesthesia of the tympanic membrane.
Patients came back for 3 further follow-up visits on Days 3, 7, 30, and 90.
Glass vials containing 0.7 mL of the gel formulation were provided for each treatment visit of which 0.25 mL were used for treatment.

Arm type	Experimental
Investigational medicinal product name	JNK inhibitor (D-JNKI-1)
Investigational medicinal product code	AM-111
Other name	
Pharmaceutical forms	Gel for injection
Routes of administration	Intratympanic use

Dosage and administration details:

Single intratympanic application of AM-111 2.0 mg/mL (0.25 mL). In case of bilateral AAT, only the worse affected ear was treated.

Arm title	Placebo pooled

Arm description:

The study consisted of 2 dose cohorts each randomised individually against placebo in a 2:1 ratio. In the results presentation the 2 placebo groups from the 2 cohorts were pooled and are presented as 1 pooled placebo group.

Study drug (gel formulation) was administered on Day 0 by intratympanic injection under local anesthesia of the tympanic membrane.
Patients came back for 3 further follow-up visits on Days 3, 7, 30, and 90.
Glass vials containing 0.7 mL of the gel formulation were provided for each treatment visit of which 0.25 mL were used for treatment.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel for injection
Routes of administration	Intratympanic use

Dosage and administration details:

0.25 mL of gel without active were injected. In case of bilateral AAT, only the worse affected ear was treated.

Number of subjects in period 1	AM-111 0.4 mg/mL	AM-111 2.0 mg/mL	Placebo pooled
Started	68	70	72
Completed	61	62	66
Not completed	7	8	6
Refused/Unable to attend visit(s)	5	2	3
Consent withdrawn by subject	-	5	1
Reason unknown	2	1	-
Change of Residence	-	-	1
Lost to follow-up	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	AM-111 0.4 mg/mL

Reporting group description:

Study drug (gel formulation) was administered on Day 0 by intratympanic injection under local anesthesia of the tympanic membrane.
Patients came back for 3 further follow-up visits on Days 3, 7, 30, and 90.
Glass vials containing 0.7 mL of the gel formulation were provided for each treatment visit of which 0.25 mL were used for treatment.

Reporting group title	AM-111 2.0 mg/mL

Reporting group description:

Study drug (gel formulation) was administered on Day 0 by intratympanic injection under local anesthesia of the tympanic membrane.
Patients came back for 3 further follow-up visits on Days 3, 7, 30, and 90.
Glass vials containing 0.7 mL of the gel formulation were provided for each treatment visit of which 0.25 mL were used for treatment.

Reporting group title	Placebo pooled

Reporting group description:

The study consisted of 2 dose cohorts each randomised individually against placebo in a 2:1 ratio. In the results presentation the 2 placebo groups from the 2 cohorts were pooled and are presented as 1 pooled placebo group.

Study drug (gel formulation) was administered on Day 0 by intratympanic injection under local anesthesia of the tympanic membrane.
Patients came back for 3 further follow-up visits on Days 3, 7, 30, and 90.
Glass vials containing 0.7 mL of the gel formulation were provided for each treatment visit of which 0.25 mL were used for treatment.

Reporting group values	AM-111 0.4 mg/mL	AM-111 2.0 mg/mL	Placebo pooled
Number of subjects	68	70	72
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)	68	70	72
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	41.1	43.9	41.7
standard deviation	± 10.9	± 10.9	± 11.8
Gender categorical Units: Subjects			
Female	24	30	28
Male	44	40	44

Reporting group values	Total		

Number of subjects	210		
Age categorical 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)	210		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	82		
Male	128		

End points

End points reporting groups

Reporting group title	AM-111 0.4 mg/mL

Reporting group description:

Study drug (gel formulation) was administered on Day 0 by intratympanic injection under local anesthesia of the tympanic membrane.
Patients came back for 3 further follow-up visits on Days 3, 7, 30, and 90.
Glass vials containing 0.7 mL of the gel formulation were provided for each treatment visit of which 0.25 mL were used for treatment.

Reporting group title	AM-111 2.0 mg/mL

Reporting group description:

Study drug (gel formulation) was administered on Day 0 by intratympanic injection under local anesthesia of the tympanic membrane.
Patients came back for 3 further follow-up visits on Days 3, 7, 30, and 90.
Glass vials containing 0.7 mL of the gel formulation were provided for each treatment visit of which 0.25 mL were used for treatment.

Reporting group title	Placebo pooled

Reporting group description:

The study consisted of 2 dose cohorts each randomised individually against placebo in a 2:1 ratio. In the results presentation the 2 placebo groups from the 2 cohorts were pooled and are presented as 1 pooled placebo group.

Study drug (gel formulation) was administered on Day 0 by intratympanic injection under local anesthesia of the tympanic membrane.
Patients came back for 3 further follow-up visits on Days 3, 7, 30, and 90.
Glass vials containing 0.7 mL of the gel formulation were provided for each treatment visit of which 0.25 mL were used for treatment.

Primary: Absolute improvement of pure tone average (PTA)

End point title	Absolute improvement of pure tone average (PTA)

End point description:

The absolute improvement of PTA given in dB between Day 0 and Day 7 based on the average of the three most affected contiguous frequencies.

End point type	Primary

End point timeframe:

Day 0 to Day 7.

End point values	AM-111 0.4 mg/mL	AM-111 2.0 mg/mL	Placebo pooled	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	64	71	
Units: dB				
arithmetic mean (standard deviation)	28.1 (± 17.7)	27.7 (± 15.6)	24 (± 16)	

Statistical analyses

Statistical analysis title	Absolute Change in PTA (dB) from baseline to Day 7
Statistical analysis description: Global comparison with analysis set "valid for efficacy" was used.	
Comparison groups	Placebo pooled v AM-111 2.0 mg/mL
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.611
Method	ANCOVA
Parameter estimate	Mean difference (final values)

Statistical analysis title	Absolute Change in PTA (dB) from baseline to Day 7
Statistical analysis description: Global comparison with analysis set "valid for efficacy" was used.	
Comparison groups	AM-111 0.4 mg/mL v Placebo pooled
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.203
Method	ANCOVA
Parameter estimate	Mean difference (final values)

Primary: Co-primary: Relative Change in PTA (%)	
End point title	Co-primary: Relative Change in PTA (%)
End point description: Relative changes from baseline in (%)	
End point type	Primary
End point timeframe: Day 0 to Day 7	

End point values	AM-111 0.4 mg/mL	AM-111 2.0 mg/mL	Placebo pooled	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	64	71	
Units: percentage				
arithmetic mean (standard deviation)	61.1 (± 37.5)	49.6 (± 44.5)	57.6 (± 40.3)	

Statistical analyses

Statistical analysis title	Relative Change Placebo pooled vs AM-111 2.0 mg/mL

Statistical analysis description: Valid for efficacy analysis set was used.	
Comparison groups	AM-111 2.0 mg/mL v Placebo pooled
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	ANCOVA

Statistical analysis title	Relative Change Placebo pooled vs AM-111 0.4 mg/mL
Statistical analysis description: Valid for efficacy analysis set was used.	
Comparison groups	AM-111 0.4 mg/mL v Placebo pooled
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5
Method	ANCOVA

Primary: Co-primary: Fequency complete recovery	
End point title	Co-primary: Fequency complete recovery
End point description: Subjects with complete recovery were counted.	
End point type	Primary
End point timeframe: Day 0 to Day 7	

End point values	AM-111 0.4 mg/mL	AM-111 2.0 mg/mL	Placebo pooled	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	64	71	
Units: subjects				
Complete recovery	27	24	33	
without complete recovery	35	40	38	

Statistical analyses

Statistical analysis title	Complete recovery rate
Statistical analysis description: Valid for Efficacy analysis set was used.	
Comparison groups	AM-111 2.0 mg/mL v Placebo pooled

Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3
Method	Regression, Logistic

Statistical analysis title	Complete recovery rate

Statistical analysis description:

Valid for Efficacy analysis set was used.

Comparison groups	Placebo pooled v AM-111 0.4 mg/mL
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.55
Method	Regression, Logistic

Primary: Safety: Frequency of patients with clinically significant hearing loss in the treated ear

End point title	Safety: Frequency of patients with clinically significant hearing loss in the treated ear

End point description:

The primary safety endpoint was defined as the number of subjects with clinically significant hearing loss, defined as deterioration of hearing thresholds of ≥10 dB at the average of any 3 contiguous test frequencies, in the treated ear from baseline to Day 7.
Analysis performed on Valid for Safety group.

End point type	Primary

End point timeframe:

Day 0 to Day 7

End point values	AM-111 0.4 mg/mL	AM-111 2.0 mg/mL	Placebo pooled	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62[1]	68	67	
Units: number patients	4	5	5	

Notes:

[1] - number of patients with significant clinically hearing loss is shown, same for all reporting groups

Statistical analyses

Statistical analysis title	Comparison - frequency of significant hearing Loss

Statistical analysis description:

Comparison of subjects with clinically significant hearing loss in the treated ear.
Only within-cohort data were used.
Valid for Safety data set is used.

Comparison groups	Placebo pooled v AM-111 2.0 mg/mL

Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

Statistical analysis title	Comparison - frequency of significant hearing Loss

Statistical analysis description:

Comparison of subjects with clinically significant hearing loss in the treated ear.
Only within-cohort data were used.
Valid for Safety data set is used.

Comparison groups	Placebo pooled v AM-111 0.4 mg/mL
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.69
Method	Fisher exact

Other pre-specified: Improvement in Speech Discrimination Score (SDS) (all)

End point title	Improvement in Speech Discrimination Score (SDS) (all)

End point description:

Average improvement in SDS between baseline and Day 7. Words were presented at 80 dB stimulus level.

End point type	Other pre-specified

End point timeframe:

Day 0 to Day 7

End point values	AM-111 0.4 mg/mL	AM-111 2.0 mg/mL	Placebo pooled	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	64	69	
Units: percent of correctly discriminated words				
arithmetic mean (standard deviation)	18.8 (± 29.6)	12.5 (± 23.4)	8 (± 20.7)	

Statistical analyses

Statistical analysis title	Absolute Change in SDS at 80 dB
Comparison groups	Placebo pooled v AM-111 2.0 mg/mL

Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.15
Method	ANCOVA

Statistical analysis title	Absolute Change in SDS at 80 dB
Comparison groups	Placebo pooled v AM-111 0.4 mg/mL
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.028
Method	ANCOVA

Post-hoc: Subgroup analysis: Absolute improvement of pure tone average (PTA) - severe to profound hearing loss

End point title	Subgroup analysis: Absolute improvement of pure tone average (PTA) - severe to profound hearing loss

End point description:

Due to unexpected high spontaneous recovery in mild to moderate hearing loss cases, an additional analysis on the subgroup with severe to profound hearing loss was performed.

End point type	Post-hoc

End point timeframe:

Day 0 - Day 7

End point values	AM-111 0.4 mg/mL	AM-111 2.0 mg/mL	Placebo pooled	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	33	30	
Units: dB				
arithmetic mean (standard deviation)	28.6 (± 22.6)	24.6 (± 20.7)	17.2 (± 18.3)	

Statistical analyses

Statistical analysis title	Absolute Change in PTA in profound to severe HL

Statistical analysis description:

Subgroup analysis in patients with profound to severe hearing loss on Valid for Efficacy analysis set.

Comparison groups	Placebo pooled v AM-111 0.4 mg/mL

Number of subjects included in analysis	59
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.017
Method	ANCOVA

Statistical analysis title	Absolute Change in PTA in profound to severe HL

Statistical analysis description:

Subgroup analysis in patients with profound to severe hearing loss on Valid for Efficacy analysis set.

Comparison groups	AM-111 2.0 mg/mL v Placebo pooled
Number of subjects included in analysis	63
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.32
Method	ANCOVA

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline to end of study at all visits.

Adverse event reporting additional description:

The occurrence of a treatment emergent adverse event in the same subject more than once was counted only once for non-serious adverse events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	AM-111 0.4 mg/mL
Reporting group description: -	
Reporting group title	AM-111 2.0 mg/mL
Reporting group description: -	
Reporting group title	Placebo pooled
Reporting group description: -	

Serious adverse events	AM-111 0.4 mg/mL	AM-111 2.0 mg/mL	Placebo pooled
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 68 (5.88%)	3 / 70 (4.29%)	2 / 72 (2.78%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Neurosurgery			
subjects affected / exposed	0 / 68 (0.00%)	1 / 70 (1.43%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Deafness neurosensory			
subjects affected / exposed	3 / 68 (4.41%)	1 / 70 (1.43%)	2 / 72 (2.78%)
occurrences causally related to treatment / all	0 / 3	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Abortion spontaneous			

subjects affected / exposed	0 / 68 (0.00%)	1 / 70 (1.43%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder			
subjects affected / exposed	1 / 68 (1.47%)	0 / 70 (0.00%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	AM-111 0.4 mg/mL	AM-111 2.0 mg/mL	Placebo pooled
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 68 (36.76%)	27 / 70 (38.57%)	27 / 72 (37.50%)
Injury, poisoning and procedural complications			
Incision site complications			
subjects affected / exposed	2 / 68 (2.94%)	2 / 70 (2.86%)	3 / 72 (4.17%)
occurrences (all)	2	2	3
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 68 (2.94%)	0 / 70 (0.00%)	2 / 72 (2.78%)
occurrences (all)	2	0	2
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 68 (0.00%)	0 / 70 (0.00%)	2 / 72 (2.78%)
occurrences (all)	0	0	2
Ear and labyrinth disorders			
Hearing impaired			
subjects affected / exposed	15 / 68 (22.06%)	15 / 70 (21.43%)	14 / 72 (19.44%)
occurrences (all)	15	15	14
Tinnitus			
subjects affected / exposed	7 / 68 (10.29%)	7 / 70 (10.00%)	6 / 72 (8.33%)
occurrences (all)	7	7	6
Ear Pain			

subjects affected / exposed	1 / 68 (1.47%)	2 / 70 (2.86%)	1 / 72 (1.39%)
occurrences (all)	1	2	1
Ear Discomfort			
subjects affected / exposed	2 / 68 (2.94%)	0 / 70 (0.00%)	1 / 72 (1.39%)
occurrences (all)	2	0	1
Vertigo			
subjects affected / exposed	0 / 68 (0.00%)	1 / 70 (1.43%)	2 / 72 (2.78%)
occurrences (all)	0	1	2
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 68 (0.00%)	2 / 70 (2.86%)	0 / 72 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 68 (0.00%)	2 / 70 (2.86%)	0 / 72 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Rhinitis			
subjects affected / exposed	2 / 68 (2.94%)	1 / 70 (1.43%)	1 / 72 (1.39%)
occurrences (all)	2	1	1
Influenza			
subjects affected / exposed	0 / 68 (0.00%)	2 / 70 (2.86%)	1 / 72 (1.39%)
occurrences (all)	0	2	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 May 2009	Modification of inclusion criteria: - Average hearing loss of at least 30 dB in the 3 most affected contiguous frequencies instead of ≥ 30 dB at each of the 3 frequencies. - Option to determine the hearing loss against the age and gender adjusted ISO tables and no longer only against the contralateral ear or against a pre-existing audiogram. - Inclusion of bilateral hearing loss resulting from noise trauma. Modification of exclusion criteria: - Requirement of pre-existing audiogram to document history of asymmetric hearing before ASNHL dropped.
03 November 2010	- Change of concentration for second cohort from 6.0 to 0.4 mg/mL; correspondingly waiver of safety and tolerability review prior to start of second cohort (no patient was dosed with 6.0 mg/mL). - Requirement for ABR measurements prior to study inclusion added to help diagnose retrocochlear lesions. - Clarification of conditions for prednisolone reserve therapy. - Comprehensive revision of the statistics section, including: Definition of statistical analysis sets; Imputation of missing values; Endpoint model; Test hypotheses; Adjustment for multiple testing of efficacy endpoints.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
30 October 2009	Observation of an impurity in stability testing. Batches were replaced.	02 December 2009

Notes:

Limitations and caveats

None reported