



Clinical trial results:

A multicentre, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of 2 dose regimens of orally administered SENS-111 (100mg and 200mg) given during 4 days in patients suffering from Acute Unilateral Vestibulopathy

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2016-003927-45 |
| Trial protocol | DE CZ HU ES PL IT |
| Global end of trial date | 15 October 2019 |

Results information

| | |
|-----------------------------------|--|
| Result version number | v1 (current) |
| This version publication date | 12 August 2020 |
| First version publication date | 12 August 2020 |
| Summary attachment (see zip file) | SENS-111-201 CSR synopsis (SENS111-201 CSR Synopsis 12May20.pdf) |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | SENS-111-201 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03110458 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Sensorion SA |
| Sponsor organisation address | 375 rue du Professeur Joseph Blayac, Montpellier, France, 34080 |
| Public contact | Judith LAREDO, Sensorion SA, +33 434087116, judith.laredo@sensorion-pharma.com |
| Scientific contact | Judith LAREDO, Sensorion SA, +33 434087116, judith.laredo@sensorion-pharma.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 | 15 November 2019 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 October 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of SENS-111 in Acute Unilateral Vestibulopathy (AUV)

Protection of trial subjects:

In exceptional circumstances, when the patient was presenting with a severe, unbearable vertigo lasting more than 4 days, a rescue medication could be given to the patient from Day 5 and onwards.

Background therapy:

No background therapy.

Evidence for comparator:

There is no approved therapy for AUV. Many patients are severely impaired by vertigo, nausea and vomiting in the acute phase: these symptoms are major targets for treatment. Nausea and vomiting are usually treated with antihistamins, mostly dimenhydrinate or even benzodiazepines in severe cases which induce sedation. The effects of corticosteroids and vestibular exercises are still debated. Those treatment were not permitted in the study.

| | |
|---|----------------|
| Actual start date of recruitment | 16 August 2017 |
| 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 | Czech Republic: 2 |
| Country: Number of subjects enrolled | France: 3 |
| Country: Number of subjects enrolled | Germany: 31 |
| Country: Number of subjects enrolled | Hungary: 5 |
| Country: Number of subjects enrolled | Israel: 34 |
| Country: Number of subjects enrolled | Italy: 2 |
| Country: Number of subjects enrolled | Korea, Republic of: 29 |
| Country: Number of subjects enrolled | United States: 1 |
| Worldwide total number of subjects | 107 |
| EEA total number of subjects | 43 |

Notes:

Subjects enrolled per age group

| | |
|--|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| | |
|--|----|
| wk | |
| 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) | 92 |
| From 65 to 84 years | 15 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The date of first informed consent was 16 August 2017. A total of 134 subjects were screened in 8 countries worldwide and 94 subjects overall out of the 107 subjects in the ITT population completed the study.

Pre-assignment

Screening details:

Out of the 134 participants screened for the trial, 27 were screen failures and were not randomized and 107 participants were randomized onto the trial.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | overall trial (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 | SENS-111 100mg |

Arm description:

1 x 100mg Oral Dispersible Tablet + 1 placebo Oral Dispersible Tablet

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | SENS-111 100mg |
| Investigational medicinal product code | SENS-111 100mg |
| Other name | |
| Pharmaceutical forms | Orodispersible tablet |
| Routes of administration | Oral use |

Dosage and administration details:

SENS-111 100mg is presented as 1 Oral Dispersible Tablet of SENS-111 100mg + 1 Oral Dispersible Tablet of placebo given twice on Day 1, second intake given approximately 12 hours (9 to 15 hours) after the first intake and thereafter given once daily on Days 2 to 5 inclusive. The corresponding total dose will be 500 mg for the entire study.

Administration Route: The tablet should not be swallowed immediately, nor taken with water. The tablet should be kept in the mouth for a few seconds until dispersion is complete.
There is no food restriction.

| | |
|------------------|----------------|
| Arm title | SENS-111 200mg |
|------------------|----------------|

Arm description:

2 x 100mg Oral Dispersible Tablets

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | SENS-111 200 mg |
| Investigational medicinal product code | SENS-111 200 mg |
| Other name | |
| Pharmaceutical forms | Orodispersible tablet |
| Routes of administration | Oral use |

Dosage and administration details:

SENS-111 200mg is presented as 2 Oral Dispersible Tablet of SENS-111 100mg given twice on Day 1, second intake given approximately 12 hours (9 to 15 hours) after the first intake and thereafter given once daily on Days 2 to 5 inclusive. The corresponding total dose will be 1000 mg for the entire study.

Administration Route: The tablet should not be swallowed immediately, nor taken with water. The tablet should be kept in the mouth for a few seconds until dispersion is complete.

There is no food restriction.

| | |
|--|-----------------------|
| Arm title | Placebo |
| Arm description: 2 placebo Oral Dispersible Tablets | |
| Arm type | Placebo |
| Investigational medicinal product name | placebo |
| Investigational medicinal product code | placebo |
| Other name | |
| Pharmaceutical forms | Orodispersible tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo is presented as 2 Oral Dispersible Tablets of placebo given twice on Day 1, second intake given approximately 12 hours (9 to 15 hours) after the first intake and thereafter given once daily on Days 2 to 5 inclusive. The corresponding total dose will be 0 mg for the entire study.

Administration Route: The tablet should not be swallowed immediately, nor taken with water. The tablet should be kept in the mouth for a few seconds until dispersion is complete.
There is no food restriction.

| Number of subjects in period 1 | SENS-111 100mg | SENS-111 200mg | Placebo |
|---------------------------------------|----------------|----------------|---------|
| Started | 37 | 36 | 34 |
| Completed | 31 | 32 | 31 |
| Not completed | 6 | 4 | 3 |
| Consent withdrawn by subject | 3 | 1 | 1 |
| Adverse event, non-fatal | - | 1 | - |
| not severe vertigo | - | - | 1 |
| other | 2 | 2 | 1 |
| Protocol deviation | 1 | - | - |

Baseline characteristics

Reporting groups

| | |
|---|----------------|
| Reporting group title | SENS-111 100mg |
| Reporting group description: 1 x 100mg Oral Dispersible Tablet + 1 placebo Oral Dispersible Tablet | |
| Reporting group title | SENS-111 200mg |
| Reporting group description: 2 x 100mg Oral Dispersible Tablets | |
| Reporting group title | Placebo |
| Reporting group description: 2 placebo Oral Dispersible Tablets | |

| Reporting group values | SENS-111 100mg | SENS-111 200mg | Placebo |
|------------------------------------|----------------|----------------|---------|
| Number of subjects | 37 | 36 | 34 |
| Age categorical Units: Subjects | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| Age continuous Units: years arithmetic mean standard deviation | 49.4 ± 12.89 | 51.6 ± 14.14 | 51.1 ± 12.82 |
| Gender categorical Units: Subjects | | | |
| Female | 14 | 8 | 11 |
| Male | 23 | 28 | 23 |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 0 | 0 | 0 |
| Not Hispanic or Latino | 20 | 21 | 19 |
| Not Reported | 16 | 15 | 15 |
| Unknown | 1 | 0 | 0 |
| Body Weight Units: kilogram(s) arithmetic mean standard deviation | 82.2 ± 22.10 | 81.6 ± 18.9 | 80.1 ± 16.37 |

| Reporting group values | Total | | |
|------------------------------------|-------|--|--|
| Number of subjects | 107 | | |
| Age categorical Units: Subjects | | | |

| | | | |
|---|---|--|--|
| Age continuous Units: years arithmetic mean standard deviation | - | | |
|---|---|--|--|

| | | | |
|------------------------|----|--|--|
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 33 | | |
| Male | 74 | | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 0 | | |
| Not Hispanic or Latino | 60 | | |
| Not Reported | 46 | | |
| Unknown | 1 | | |
| Body Weight | | | |
| Units: kilogram(s) | | | |
| arithmetic mean | | | |
| standard deviation | - | | |

End points

End points reporting groups

| | |
|---|----------------|
| Reporting group title | SENS-111 100mg |
| Reporting group description: 1 x 100mg Oral Dispersible Tablet + 1 placebo Oral Dispersible Tablet | |
| Reporting group title | SENS-111 200mg |
| Reporting group description: 2 x 100mg Oral Dispersible Tablets | |
| Reporting group title | Placebo |
| Reporting group description: 2 placebo Oral Dispersible Tablets | |

Primary: Standing vertigo intensity

| | |
|---|----------------------------|
| End point title | Standing vertigo intensity |
| End point description: The primary efficacy endpoint was the Area Under Curve (AUC) for the vertigo intensity measured by the Vertigo Intensity Visual Analogue Scale (VI-VAS) in standing position over the 4 treatment days (8 post-baseline assessments). The vertigo Intensity VAS is a non-anchored 10cm horizontal line. Patients were asked to rate the intensity of their vertigo making a vertical mark crossing the horizontal 10 cm line to indicate the severity from 0-100 when 0 indicates no severity and 100 indicates worse severity | |
| End point type | Primary |
| End point timeframe: during 4 days of treatment | |

| End point values | SENS-111 100mg | SENS-111 200mg | Placebo | |
|--|-----------------------|-----------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 34 | 35 | 31 | |
| Units: Vertigo Intensity Visual Analogue Scale | | | | |
| arithmetic mean (standard error) | 165.10 (\pm 71.02) | 155.10 (\pm 83.06) | 136.60 (\pm 62.61) | |

Statistical analyses

| | |
|----------------------------|-------------------------------|
| Statistical analysis title | SENS-111 100mg versus placebo |
| Comparison groups | SENS-111 100mg v Placebo |

| | |
|---|---------------|
| Number of subjects included in analysis | 65 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8466 |
| Method | ANCOVA |

| | |
|---|---|
| Statistical analysis title | SENS-111 pooled versus placebo |
| Comparison groups | SENS-111 100mg v SENS-111 200mg v Placebo |
| Number of subjects included in analysis | 100 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8411 |
| Method | ANCOVA |

| | |
|---|-------------------------------|
| Statistical analysis title | SENS-111 200mg versus placebo |
| Comparison groups | SENS-111 200mg v Placebo |
| Number of subjects included in analysis | 66 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7677 |
| Method | ANCOVA |

Secondary: Worst spontaneous vertigo intensity

| | |
|--|-------------------------------------|
| End point title | Worst spontaneous vertigo intensity |
| End point description: | |
| Worst spontaneous vertigo intensity measured by the AUC of the worst Vertigo Intensity Visual Analogue Scale (VI-VAS) over the 4 treatment days (8 post-baseline assessments). The vertigo Intensity VAS is a non-anchored 10cm horizontal line. Patients were asked to rate the intensity of their vertigo making a vertical mark crossing the horizontal 10 cm line to indicate the severity from 0-100 when 0 indicates no severity and 100 indicates worse severity | |
| End point type | Secondary |
| End point timeframe: | |
| over the 4 treatment days (Day 5) | |

| End point values | SENS-111 100mg | SENS-111 200mg | Placebo | |
|--|-------------------|-------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 31 | 32 | 27 | |
| Units: Vertigo Intensity Visual Analogue Scale | | | | |
| arithmetic mean (standard deviation) | 180.1 (± 67.20) | 170.4 (± 89.83) | 140.8 (± 64.66) | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | SENS-111 pooled versus placebo |
| Comparison groups | SENS-111 100mg v SENS-111 200mg v Placebo |
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9538 |
| Method | ANCOVA |

Secondary: Proprioception D28 (Change from Baseline of the total score of the Romberg test)

| | |
|--|--|
| End point title | Proprioception D28 (Change from Baseline of the total score of the Romberg test) |
| End point description: Change from Baseline of the total score of the six conditions of the Romberg test (in this test higher values are indicating a higher ability to stand unassisted, total minimum: 0 maximum: 6) at the end of treatment (EOT) (Day 5) and at the end of study (EOS) (Day 28) | |
| End point type | Secondary |
| End point timeframe: End of treatment (Day 5) to End of study (Day 28). | |

| End point values | SENS-111 100mg | SENS-111 200mg | Placebo | |
|--------------------------------------|-------------------|-------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 30 | 33 | 26 | |
| Units: absolute value Romberg test | | | | |
| arithmetic mean (standard deviation) | 2.70 (± 1.60) | 3.00 (± 1.64) | 3.20 (± 1.46) | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | SENS-111 pooled versus placebo |
| Comparison groups | SENS-111 100mg v SENS-111 200mg v Placebo |

| | |
|---|---------------|
| Number of subjects included in analysis | 89 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.393 |
| Method | ANCOVA |

Secondary: Vestibular spontaneous nystagmus D28

| | |
|--|--------------------------------------|
| End point title | Vestibular spontaneous nystagmus D28 |
| End point description: Change from Baseline of the Peak Slow Phase Velocity of the Peripheral Vestibular Spontaneous Nystagmus, measured by Oculography in Darkness at End of treatment (Day 5) and End of Study (Day 28) | |
| End point type | Secondary |
| End point timeframe: 28 days compared to baseline | |

| End point values | SENS-111 100mg | SENS-111 200mg | Placebo | |
|--------------------------------------|-------------------|-------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 26 | 25 | 23 | |
| Units: degrees per second | | | | |
| arithmetic mean (standard deviation) | -4.80 (± 15.10) | -7.9 (± 12.76) | -7.7 (± 11.59) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Nausea severity

| | |
|---|-----------------|
| End point title | Nausea severity |
| End point description: Nausea Severity measured by the Area under the Curve of the Nausea Intensity Visual Analogue Scale (NI-VAS) over the 4 Treatment Days (8 Post-baseline Assessments). Patients were asked to rate the intensity of their nausea making a vertical mark crossing the 10 cm line to indicate the severity from 0-100 when 0 indicates no severity and 100 indicates worse severity. | |
| End point type | Secondary |
| End point timeframe: over the 4 Treatment Days (Day 5) | |

| End point values | SENS-111 100mg | SENS-111 200mg | Placebo | |
|---|-------------------|-------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 34 | 35 | 31 | |
| Units: Nausea Intensity Visual Analogue Scale | | | | |
| arithmetic mean (standard deviation) | 93.00 (± 78.39) | 91.50 (± 79.73) | 92.60 (± 57.28) | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | SENS-111 pooled versus placebo |
| Comparison groups | SENS-111 100mg v SENS-111 200mg v Placebo |
| Number of subjects included in analysis | 100 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5324 |
| Method | ANCOVA |

Secondary: Proprioception D5 (Change from Baseline of the total score of the Romberg test)

| | |
|------------------------|--|
| End point title | Proprioception D5 (Change from Baseline of the total score of the Romberg test) |
| End point description: | Change from Baseline of the total score of the six conditions of the Romberg test (in this test higher values are indicating a higher ability to stand unassisted, total minimum: 0 maximum: 6) at the end of treatment (EOT) (Day 5) and at the end of study (EOS) (Day 28) |
| End point type | Secondary |
| End point timeframe: | After 4 days of treatment (D5) |

| End point values | SENS-111 100mg | SENS-111 200mg | Placebo | |
|--------------------------------------|-------------------|-------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 32 | 32 | 26 | |
| Units: absolute value Romberg test | | | | |
| arithmetic mean (standard deviation) | 2.10 (± 1.46) | 2.00 (± 1.79) | 2.40 (± 1.45) | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | SENS-111 pooled versus placebo |
| Comparison groups | SENS-111 100mg v SENS-111 200mg v Placebo |

| | |
|---|---------------|
| Number of subjects included in analysis | 90 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3166 |
| Method | ANCOVA |

Secondary: Vestibular spontaneous nystagmus D5

| | |
|--|-------------------------------------|
| End point title | Vestibular spontaneous nystagmus D5 |
| End point description: Change from Baseline of the Peak Slow Phase Velocity of the Peripheral Vestibular Spontaneous Nystagmus, measured by Oculography in Darkness at End of treatment (Day 5) and end of study (EOS) (Day 28) | |
| End point type | Secondary |
| End point timeframe: after 4 days of treatment (D5) | |

| End point values | SENS-111 100mg | SENS-111 200mg | Placebo | |
|--------------------------------------|-------------------|-------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 24 | 27 | 25 | |
| Units: degrees per second | | | | |
| arithmetic mean (standard deviation) | -2.80 (± 10.86) | -3.0 (± 6.72) | -3.50 (± 5.32) | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

28 days

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------|
| Reporting group title | SENS-111 100mg |
|-----------------------|----------------|

Reporting group description:

Treatment emergent adverse events are displayed.

A total of 9 subjects were affected by non serious adverse events. With the frequency threshold of 5%, 4 subjects reported non-serious adverse events.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Treatment emergent adverse events are displayed

A total of 12 subjects were affected by non serious adverse events. With the frequency threshold of 5%, 7 subjects reported non-serious adverse events.

| | |
|-----------------------|----------------|
| Reporting group title | SENS-111 200mg |
|-----------------------|----------------|

Reporting group description:

Treatment emergent adverse events are displayed

A total of 14 subjects were affected by non serious adverse events. With the frequency threshold of 5%, 5 subjects reported non-serious adverse events.

| Serious adverse events | SENS-111 100mg | Placebo | SENS-111 200mg |
|---|----------------|----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 32 (0.00%) | 1 / 36 (2.78%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Diverticular perforation | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 0 / 32 (0.00%) | 1 / 36 (2.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | SENS-111 100mg | Placebo | SENS-111 200mg |
|---|-----------------|-----------------|-----------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 4 / 36 (11.11%) | 7 / 32 (21.88%) | 5 / 36 (13.89%) |

| | | | |
|---|---------------------|----------------------|----------------------|
| Injury, poisoning and procedural complications Extra dose administered subjects affected / exposed occurrences (all) | 0 / 36 (0.00%) 0 | 2 / 32 (6.25%) 2 | 0 / 36 (0.00%) 0 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 2 / 36 (5.56%) 3 | 7 / 32 (21.88%) 8 | 4 / 36 (11.11%) 6 |
| Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all) | 0 / 36 (0.00%) 0 | 0 / 32 (0.00%) 0 | 2 / 36 (5.56%) 2 |
| Metabolism and nutrition disorders Folate deficiency subjects affected / exposed occurrences (all) | 2 / 36 (5.56%) 2 | 0 / 32 (0.00%) 0 | 0 / 36 (0.00%) 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 09 February 2017 | <p>This amendment was prepared to address Grounds for Non-acceptance raised during the Voluntary Harmonisation Procedure and included the following changes:</p> <ul style="list-style-type: none">- Exclusion criterion no. 28 was amended to exclude subjects (male or female) who were unwilling to use 1 of the highly effective contraception therapies listed in the exclusion criteria. In addition, an appendix was added to the protocol to provide complete guidance on highly effective birth control. Also the wording "effective contraception" was changed to "highly effective contraception" throughout the protocol.- Inclusion criterion no. 1 was amended to include an upper age limit and to provide a justification for the selected upper age limit. The sponsor proposed an upper age limit of 75 years as being most representative of the target subject population.- a new section Unblinding Procedure was added to the protocol. A complete discussion of unblinding procedures using the Interactive Web Response System was presented in this new section- protocol's withdrawal criteria was modified to include the worsening of nausea or vertigo as demonstrated on 2 successive VAS scale scores. Additionally, the criteria were expanded to include the onset of new neurological symptoms and hearing loss.- some statement were added indicating that:<ul style="list-style-type: none">*biological samples were to be analyzed locally and destroyed after the analyses. No further uses of the samples were planned for additional research.* no change or amendment to the protocol would be implemented before approval was received by the regulatory authority and ethics committees.* no protocol waivers were to be accepted and any protocol deviation will be assessed by the sponsor. In the event of breach of fundamental obligations including but not limited to breach of the clinical trial protocol, breach of the applicable laws and regulations or breach of the ICH guideline on GCP, the sponsor will report major noncompliance to the Regulatory Authorities |
| 08 September 2017 | <ul style="list-style-type: none">• Exclusion criterion no. 22 on contraception was amendment to indicate that contraception had to be used for at least 3 months after the last IMP intake• at some specific sites, an ancillary test using the Caloric test or vHIT were conducted• clarification that consent and screening were to be done no more than 12 hours apart |
| 05 November 2018 | <ul style="list-style-type: none">- clarification that around 38 sites in Europe, Israel, USA, and South Korea were planned to be involved in the study- update of sample size calculation so that the number of randomized subjects was reduced to 105 (35 subjects per treatment arm)- Exclusion criterion no. 16 updated so to exclude subjects if they had taken more than 3 doses of the listed concomitant medications- The ECG assessment was moved from V2 to V1 (Screening) and Romberg tests were added at V2, V3, and V4- "Unrelated" was added as an assessment option of AE relationship |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported