



## Clinical trial results:

**Phase III study, double blind, placebo controlled, to evaluate the efficacy and the safety of an omega-3 based drug, in patients with primary tinnitus.**

### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2015-003514-24  |
| Trial protocol           | IT              |
| Global end of trial date | 17 October 2018 |

### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 27 April 2022 |
| First version publication date | 27 April 2022 |

### Trial information

#### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | OLEV01/2015 |
|-----------------------|-------------|

#### Additional study identifiers

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

Notes:

#### Sponsors

|                              |                                                                |
|------------------------------|----------------------------------------------------------------|
| Sponsor organisation name    | IBSA Farmaceutici Italia srl                                   |
| Sponsor organisation address | Via Martiri di Cefalonia, 2, Lodi, Italy, 26900                |
| Public contact               | CRO, Informa PRO S.r.l., +39 065758926, segreteria@informa.pro |
| Scientific contact           | CRO, Informa PRO S.r.l., +39 065758926, segreteria@informa.pro |

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? | Yes              |
| Primary completion date                              | 17 October 2018  |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 17 October 2018  |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

Evaluation of the efficacy and safety of Olevia (omega-3 polyunsaturated acid based drug) in both genders patients affected by primary tinnitus.

Protection of trial subjects:

Patients were monitored for any possible adverse events occurred between each visits.

Background therapy: -

Evidence for comparator:

NA

|                                                           |                   |
|-----------------------------------------------------------|-------------------|
| Actual start date of recruitment                          | 05 September 2016 |
| Long term follow-up planned                               | No                |
| Independent data monitoring committee (IDMC) involvement? | No                |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |           |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Italy: 99 |
| Worldwide total number of subjects   | 99        |
| EEA total number of subjects         | 99        |

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)                      | 80 |
| From 65 to 84 years                       | 19 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

First Patient First Visit: 05-09-2016; Last Patient First Visit: 27-03-2018; Last Patient Last Visit: 17-10-2018

The trial was conducted on 5 Sites: Site 01 - Salerno; Site 02 - Bologna; Site 03- Catanzaro; Site 04- Pisa; Site 05- Torino.

### Pre-assignment

Screening details:

14 subjects did not meet the Inclusion/Exclusion Criteria.

### Pre-assignment period milestones

|                              |    |
|------------------------------|----|
| Number of subjects started   | 99 |
| Number of subjects completed | 99 |

### Period 1

|                              |                           |
|------------------------------|---------------------------|
| Period 1 title               | Baseline (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 |
|------------------------------|-----|

|                  |          |
|------------------|----------|
| <b>Arm title</b> | Arm A PP |
|------------------|----------|

Arm description:

Subjects treated with Olevia

|                                        |                |
|----------------------------------------|----------------|
| Arm type                               | Experimental   |
| Investigational medicinal product name | Olevia 1000 mg |
| Investigational medicinal product code | 042639029      |
| Other name                             | OMEGAIBSA2     |
| Pharmaceutical forms                   | Capsule, soft  |
| Routes of administration               | Oral use       |

Dosage and administration details:

2000 mg/die for the first 2 months (2 capsule); 1000 mg/die for the third month (1 capsule).

|                  |          |
|------------------|----------|
| <b>Arm title</b> | Arm B PP |
|------------------|----------|

Arm description:

Subjects treated with placebo

|                                        |               |
|----------------------------------------|---------------|
| Arm type                               | Placebo       |
| Investigational medicinal product name | Placebo       |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, soft |
| Routes of administration               | Oral use      |

Dosage and administration details:

2000 mg/die for the first 2 months (2 capsule); 1000 mg/die for the third month (1 capsule).

| <b>Number of subjects in period 1</b> | Arm A PP | Arm B PP |
|---------------------------------------|----------|----------|
| Started                               | 49       | 50       |
| Completed                             | 39       | 41       |
| Not completed                         | 10       | 9        |
| Lost to Follow up                     | 3        | 3        |
| Physician decision                    | 1        | 3        |
| Consent withdrawn by subject          | 1        | 1        |
| Adverse event, non-fatal              | 5        | -        |
| Lack of compliance                    | -        | 1        |
| Protocol deviation                    | -        | 1        |

## Baseline characteristics

### Reporting groups

|                               |          |
|-------------------------------|----------|
| Reporting group title         | Arm A PP |
| Reporting group description:  |          |
| Subjects treated with Olevia  |          |
| Reporting group title         | Arm B PP |
| Reporting group description:  |          |
| Subjects treated with placebo |          |

| Reporting group values                             | Arm A PP | Arm B PP | Total |
|----------------------------------------------------|----------|----------|-------|
| Number of subjects                                 | 49       | 50       | 99    |
| 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)                               | 41       | 42       | 83    |
| From 65-84 years                                   | 8        | 8        | 16    |
| 85 years and over                                  | 0        | 0        | 0     |
| Gender categorical                                 |          |          |       |
| Units: Subjects                                    |          |          |       |
| Female                                             | 20       | 17       | 37    |
| Male                                               | 29       | 33       | 62    |

### Subject analysis sets

|                                                           |                    |
|-----------------------------------------------------------|--------------------|
| Subject analysis set title                                | Arm A ITT          |
| Subject analysis set type                                 | Intention-to-treat |
| Subject analysis set description:                         |                    |
| Subjects with at least one efficacy parameter assessment. |                    |
| Subject analysis set title                                | Arm B ITT          |
| Subject analysis set type                                 | Intention-to-treat |
| Subject analysis set description:                         |                    |
| Subjects with at least one efficacy parameter assessment. |                    |
| Subject analysis set title                                | Arm A PP           |
| Subject analysis set type                                 | Per protocol       |
| Subject analysis set description:                         |                    |
| Subjects completed the study according to Protocol        |                    |
| Subject analysis set title                                | Arm B PP           |
| Subject analysis set type                                 | Per protocol       |
| Subject analysis set description:                         |                    |
| Subjects completed the study according to Protocol        |                    |

| <b>Reporting group values</b>                         | Arm A ITT | Arm B ITT | Arm A PP |
|-------------------------------------------------------|-----------|-----------|----------|
| Number of subjects                                    | 45        | 45        | 39       |
| Age categorical<br>Units: Subjects                    |           |           |          |
| In utero                                              | 0         | 0         | 0        |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0         | 0         | 0        |
| Newborns (0-27 days)                                  | 0         | 0         | 0        |
| Infants and toddlers (28 days-23<br>months)           | 0         | 0         | 0        |
| Children (2-11 years)                                 | 0         | 0         | 0        |
| Adolescents (12-17 years)                             | 0         | 0         | 0        |
| Adults (18-64 years)                                  | 37        | 37        | 31       |
| From 65-84 years                                      | 8         | 8         | 8        |
| 85 years and over                                     | 0         | 0         | 0        |
| Gender categorical<br>Units: Subjects                 |           |           |          |
| Female                                                | 18        | 14        | 16       |
| Male                                                  | 27        | 31        | 23       |

| <b>Reporting group values</b>                         | Arm B PP |  |  |
|-------------------------------------------------------|----------|--|--|
| Number of subjects                                    | 41       |  |  |
| Age categorical<br>Units: Subjects                    |          |  |  |
| In utero                                              | 0        |  |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0        |  |  |
| Newborns (0-27 days)                                  | 0        |  |  |
| Infants and toddlers (28 days-23<br>months)           | 0        |  |  |
| Children (2-11 years)                                 | 0        |  |  |
| Adolescents (12-17 years)                             | 0        |  |  |
| Adults (18-64 years)                                  | 34       |  |  |
| From 65-84 years                                      | 7        |  |  |
| 85 years and over                                     | 0        |  |  |
| Gender categorical<br>Units: Subjects                 |          |  |  |
| Female                                                | 12       |  |  |
| Male                                                  | 29       |  |  |

## End points

### End points reporting groups

|                                                                                                |                    |
|------------------------------------------------------------------------------------------------|--------------------|
| Reporting group title                                                                          | Arm A PP           |
| Reporting group description:<br>Subjects treated with Olevia                                   |                    |
| Reporting group title                                                                          | Arm B PP           |
| Reporting group description:<br>Subjects treated with placebo                                  |                    |
| Subject analysis set title                                                                     | Arm A ITT          |
| Subject analysis set type                                                                      | Intention-to-treat |
| Subject analysis set description:<br>Subjects with at least one efficacy parameter assessment. |                    |
| Subject analysis set title                                                                     | Arm B ITT          |
| Subject analysis set type                                                                      | Intention-to-treat |
| Subject analysis set description:<br>Subjects with at least one efficacy parameter assessment. |                    |
| Subject analysis set title                                                                     | Arm A PP           |
| Subject analysis set type                                                                      | Per protocol       |
| Subject analysis set description:<br>Subjects completed the study according to Protocol        |                    |
| Subject analysis set title                                                                     | Arm B PP           |
| Subject analysis set type                                                                      | Per protocol       |
| Subject analysis set description:<br>Subjects completed the study according to Protocol        |                    |

### Primary: Evaluation of the level of reduction of the primary tinnitus, through THI scale, in both groups.

|                                                                     |                                                                                                  |
|---------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| End point title                                                     | Evaluation of the level of reduction of the primary tinnitus, through THI scale, in both groups. |
| End point description:                                              |                                                                                                  |
| End point type                                                      | Primary                                                                                          |
| End point timeframe:<br>2 months and 3 months after baseline visit. |                                                                                                  |

| End point values            | Arm A PP        | Arm B PP        | Arm A ITT            | Arm B ITT            |
|-----------------------------|-----------------|-----------------|----------------------|----------------------|
| Subject group type          | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 39              | 41              | 45                   | 45                   |
| Units: THI                  | 24              | 22              | 27                   | 24                   |

## Statistical analyses

|                                                                           |                                           |
|---------------------------------------------------------------------------|-------------------------------------------|
| <b>Statistical analysis title</b>                                         | Evaluation of reduction in scale THI (PP) |
| Statistical analysis description:<br>Subjects reduction in scale THI (PP) |                                           |
| Comparison groups                                                         | Arm B PP v Arm A PP                       |
| Number of subjects included in analysis                                   | 80                                        |
| Analysis specification                                                    | Post-hoc                                  |
| Analysis type                                                             | non-inferiority <sup>[1]</sup>            |
| P-value                                                                   | = 0.506 <sup>[2]</sup>                    |
| Method                                                                    | Fisher exact                              |

Notes:

[1] - Two tailed test, alpha error = 0.05

[2] - p=0.506 at 3 months.

Both tests are not statistically significant

|                                                                            |                                            |
|----------------------------------------------------------------------------|--------------------------------------------|
| <b>Statistical analysis title</b>                                          | Evaluation of reduction in scale THI (ITT) |
| Statistical analysis description:<br>Subjects reduction in scale THI (ITT) |                                            |
| Comparison groups                                                          | Arm A ITT v Arm B ITT                      |
| Number of subjects included in analysis                                    | 90                                         |
| Analysis specification                                                     | Post-hoc                                   |
| Analysis type                                                              | non-inferiority <sup>[3]</sup>             |
| P-value                                                                    | = 0.671 <sup>[4]</sup>                     |
| Method                                                                     | Fisher exact                               |

Notes:

[3] - Two tailed test, alpha error = 0.05

[4] - p=0.657 at 3 months.

Both tests are not statistically significant

### Secondary: Evaluation of level of compliance to treatment through, in both groups.

|                 |                                                                         |
|-----------------|-------------------------------------------------------------------------|
| End point title | Evaluation of level of compliance to treatment through, in both groups. |
|-----------------|-------------------------------------------------------------------------|

End point description:

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

End point timeframe:

2 months and 3 months after baseline visit

| <b>End point values</b>     | Arm A PP        | Arm B PP        | Arm A ITT            | Arm B ITT            |
|-----------------------------|-----------------|-----------------|----------------------|----------------------|
| Subject group type          | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 39              | 41              | 45                   | 45                   |
| Units: questionnaire        | 39              | 40              | 43                   | 44                   |

### Statistical analyses

|                                   |                                            |
|-----------------------------------|--------------------------------------------|
| <b>Statistical analysis title</b> | evaluation of compliance between groups pp |
|-----------------------------------|--------------------------------------------|

Statistical analysis description:

evaluation of subject completing compliance

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Comparison groups                       | Arm B PP v Arm A PP            |
| Number of subjects included in analysis | 80                             |
| Analysis specification                  | Post-hoc                       |
| Analysis type                           | non-inferiority <sup>[5]</sup> |
| P-value                                 | = 1 <sup>[6]</sup>             |
| Method                                  | Fisher exact                   |

Notes:

[5] - Two tailed test, alpha error = 0.05

[6] - p value =1 at three months

both test are not staistical significant

|                                         |                                             |
|-----------------------------------------|---------------------------------------------|
| <b>Statistical analysis title</b>       | evaluation of compliance between groups ITT |
| Comparison groups                       | Arm A ITT v Arm B ITT                       |
| Number of subjects included in analysis | 90                                          |
| Analysis specification                  | Post-hoc                                    |
| Analysis type                           | non-inferiority <sup>[7]</sup>              |
| P-value                                 | = 1 <sup>[8]</sup>                          |
| Method                                  | Fisher exact                                |

Notes:

[7] - Two tailed test, alpha error = 0.05

[8] - p value =1 at three months

both test are not statistical significant

### Secondary: Evaluation of the grade of reduction of hyperacusis.

|                 |                                                      |
|-----------------|------------------------------------------------------|
| End point title | Evaluation of the grade of reduction of hyperacusis. |
|-----------------|------------------------------------------------------|

End point description:

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

End point timeframe:

2 months and 3 months after baseline visit

| End point values            | Arm A PP        | Arm B PP        | Arm A ITT            | Arm B ITT            |
|-----------------------------|-----------------|-----------------|----------------------|----------------------|
| Subject group type          | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 39              | 41              | 45                   | 45                   |
| Units: questionnaire        | 14              | 19              | 18                   | 20                   |

### Statistical analyses

|                                   |                                        |
|-----------------------------------|----------------------------------------|
| <b>Statistical analysis title</b> | Reduction in Khalfa questionnaire (PP) |
|-----------------------------------|----------------------------------------|

Statistical analysis description:

Number of subjects reduction in Khalfa questionnaire (PP)

|                   |                     |
|-------------------|---------------------|
| Comparison groups | Arm A PP v Arm B PP |
|-------------------|---------------------|

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Number of subjects included in analysis | 80                             |
| Analysis specification                  | Post-hoc                       |
| Analysis type                           | non-inferiority <sup>[9]</sup> |
| P-value                                 | = 0.372 <sup>[10]</sup>        |
| Method                                  | Fisher exact                   |

Notes:

[9] - Two tailed test, alpha error=0.05

[10] - P=0.187 at 3 months.

Both tests are not statistically significant

|                                   |                                         |
|-----------------------------------|-----------------------------------------|
| <b>Statistical analysis title</b> | Reduction in Khalfa questionnaire (ITT) |
|-----------------------------------|-----------------------------------------|

Statistical analysis description:

Number of subjects reduction in Khalfa questionnaire (ITT)

|                                         |                                 |
|-----------------------------------------|---------------------------------|
| Comparison groups                       | Arm A ITT v Arm B ITT           |
| Number of subjects included in analysis | 90                              |
| Analysis specification                  | Post-hoc                        |
| Analysis type                           | non-inferiority <sup>[11]</sup> |
| P-value                                 | = 0.831 <sup>[12]</sup>         |
| Method                                  | Fisher exact                    |

Notes:

[11] - Two tailed test, alpha error=0.05

[12] - p=0.191 at 3 months.

Both tests are not statistically significant

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

During all the study, from signature ICF to end of study.

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 24 |
|--------------------|----|

### Reporting groups

|                       |        |
|-----------------------|--------|
| Reporting group title | Olevia |
|-----------------------|--------|

Reporting group description:

Subjects treated by Olevia.

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

Reporting group description:

Subjects treated by Placebo

| <b>Serious adverse events</b>                     | Olevia         | Placebo        |  |
|---------------------------------------------------|----------------|----------------|--|
| Total subjects affected by serious adverse events |                |                |  |
| subjects affected / exposed                       | 0 / 49 (0.00%) | 0 / 51 (0.00%) |  |
| number of deaths (all causes)                     | 0              | 0              |  |
| number of deaths resulting from adverse events    | 0              | 0              |  |

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

| <b>Non-serious adverse events</b>                     | Olevia                                       | Placebo        |  |
|-------------------------------------------------------|----------------------------------------------|----------------|--|
| Total subjects affected by non-serious adverse events |                                              |                |  |
| subjects affected / exposed                           | 10 / 49 (20.41%)                             | 3 / 51 (5.88%) |  |
| Investigations                                        |                                              |                |  |
| Hypertransaminasaemia                                 | Additional description: MedDRA Cod. 10054889 |                |  |
| subjects affected / exposed                           | 1 / 49 (2.04%)                               | 0 / 51 (0.00%) |  |
| occurrences (all)                                     | 1                                            | 0              |  |
| Hypercholesterolaemia                                 | Additional description: MedDRA Cod. 10020603 |                |  |
| subjects affected / exposed                           | 1 / 49 (2.04%)                               | 1 / 51 (1.96%) |  |
| occurrences (all)                                     | 1                                            | 1              |  |
| Injury, poisoning and procedural complications        |                                              |                |  |

|                                                                                                                                                                                                                                                                              |                                               |                     |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|---------------------|--|
| Subcutaneous haematoma<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                    | Additional description: MedDRA Cod. 10022117. |                     |  |
|                                                                                                                                                                                                                                                                              | 1 / 49 (2.04%)<br>1                           | 0 / 51 (0.00%)<br>0 |  |
| Vascular disorders<br>Hypotension<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                         | Additional description: MedDRA Cod. 10021106  |                     |  |
|                                                                                                                                                                                                                                                                              | 1 / 49 (2.04%)<br>1                           | 0 / 51 (0.00%)<br>0 |  |
| Nervous system disorders<br>Paraesthesia<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                  | Additional description: MedDRA Cod. 10033987  |                     |  |
|                                                                                                                                                                                                                                                                              | 1 / 49 (2.04%)<br>1                           | 0 / 51 (0.00%)<br>0 |  |
| Ear and labyrinth disorders<br>Tinnitus<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                   | Additional description: MedDRA Cod. 10048029  |                     |  |
|                                                                                                                                                                                                                                                                              | 2 / 49 (4.08%)<br>1                           | 0 / 51 (0.00%)<br>0 |  |
| Gastrointestinal disorders<br>Abdominal pain upper<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)<br><br>Constipation<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all) | Additional description: MedDRA Cod. 10064906  |                     |  |
|                                                                                                                                                                                                                                                                              | 1 / 49 (2.04%)<br>1                           | 0 / 51 (0.00%)<br>0 |  |
|                                                                                                                                                                                                                                                                              | Additional description: MedDRA Cod. 10010774  |                     |  |
|                                                                                                                                                                                                                                                                              | 1 / 49 (2.04%)<br>1                           | 0 / 51 (0.00%)<br>0 |  |
| Skin and subcutaneous tissue disorders<br>Erythema<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)                                                                                                                        | Additional description: MedDRA Cod. 10015150  |                     |  |
|                                                                                                                                                                                                                                                                              | 1 / 49 (2.04%)<br>1                           | 0 / 51 (0.00%)<br>0 |  |
| Musculoskeletal and connective tissue disorders                                                                                                                                                                                                                              |                                               |                     |  |

|                                                                                                                 |                                              |                     |  |
|-----------------------------------------------------------------------------------------------------------------|----------------------------------------------|---------------------|--|
| Headache<br>alternative assessment type: Non-systematic<br>subjects affected / exposed<br>occurrences (all)     | Additional description: MedDRA Cod. 10028411 |                     |  |
|                                                                                                                 | 1 / 49 (2.04%)<br>1                          | 0 / 51 (0.00%)<br>0 |  |
| Metabolism and nutrition disorders<br>Hypertriglyceridaemia<br>subjects affected / exposed<br>occurrences (all) | Additional description: MedDRA Cod. 10020870 |                     |  |
|                                                                                                                 | 0 / 49 (0.00%)<br>0                          | 2 / 51 (3.92%)<br>1 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                  |
|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 24 February 2016 | 1) Background rational extension.<br>2) Added Follow Up Visit (Visit V4) 6 months after Baseline Visit.<br>3) At Drop Out section was added "Not compliance to treatment". |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported