



Clinical trial results:

A RANDOMIZED, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF CIRCADIN® TO ALLEVIATE SLEEP DISTURBANCES IN CHILDREN WITH NEURODEVELOPMENTAL DISABILITIES

Summary

| | |
|--------------------------|----------------------------|
| EudraCT number | 2013-001832-23 |
| Trial protocol | Outside EU/EEA FI GB NL FR |
| Global end of trial date | 28 February 2018 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 12 September 2018 |
| First version publication date | 12 September 2018 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | NEU_CH_7911 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01906866 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Neurim Pharmaceuticals |
| Sponsor organisation address | Habarzel 27, Tel Aviv, Israel, |
| Public contact | VP Clinical and Regulatory Affairs, Neurim Pharmaceuticals (1991) Ltd., Talin@neurim.com |
| Scientific contact | VP Clinical and Regulatory Affairs, Neurim Pharmaceuticals (1991) Ltd., talin@neurim.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000440-PIP02-11 |
| 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? | Yes |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 25 July 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 28 February 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 February 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare the treatment effect of Circadin 2/5 mg to that of placebo on sleep maintenance (total sleep time [TST]) as assessed by the Sleep and Nap Diary after 13 weeks of double-blind treatment.

Protection of trial subjects:

NA

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------------------------|
| Actual start date of recruitment | 01 November 2013 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy, Regulatory reason |
| Long term follow-up duration | 21 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Netherlands: 20 |
| Country: Number of subjects enrolled | United Kingdom: 35 |
| Country: Number of subjects enrolled | France: 7 |
| Country: Number of subjects enrolled | United States: 200 |
| Country: Number of subjects enrolled | Finland: 5 |
| Worldwide total number of subjects | 267 |
| EEA total number of subjects | 67 |

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) | 174 |
| Adolescents (12-17 years) | 93 |

| | |
|----------------------|---|
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Recruitment started on December 2013 first patient first visit was on January 2014 last patient last visit on February 28th 2018

Pre-assignment

Screening details:

A screening visit was conducted 4 weeks prior to randomization. Children who did not have a documented history of sleep hygiene and behavioral intervention at screening underwent 4 weeks of basic sleep hygiene and behavioral intervention (Weeks -4 to 0). This period also served as a wash-out period from any hypnotics; a gradual withdrawal took place

Period 1

| | |
|------------------------------|-----------------------------|
| Period 1 title | placebo run-in |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Single blind |
| Roles blinded | Subject |

Arms

| | |
|-----------|---------|
| Arm title | placebo |
|-----------|---------|

Arm description:

single blind

| | |
|--|------------|
| Arm type | Placebo |
| Investigational medicinal product name | placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Buccal use |

Dosage and administration details:

2 mini-tablets 0.5-1 hour before bedtime.

| Number of subjects in period 1 | placebo |
|--------------------------------|---------|
| Started | 267 |
| Completed | 125 |
| Not completed | 142 |
| non eligible | 142 |

Period 2

| | |
|------------------------------|-------------------------|
| Period 2 title | double blind |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |

| | |
|---------------|---|
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |
|---------------|---|

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|--------------|
| Arm title | Experimental |
|------------------|--------------|

Arm description:

Experimental product - 2 mg or 5 mg

| | |
|--|-----------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Melatonin prolonged release |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Buccal tablet |
| Routes of administration | Buccal use |

Dosage and administration details:

2 mg for the first 3 weeks double blind period. After 3 weeks of double-blind treatment, on the last day of Week 5 \pm 3 days (Visit 3), sleep variables were assessed to determine if dose modification (an increase to 5 mg) was required. Children who did not improve by 60 minutes in TST, sleep latency or both at this time were eligible for dose increase. Children then continued on 2 or 5 mg of Circadin® or placebo for the remaining 10 weeks of double-blind treatment, with an efficacy assessment visit at Week 15 (Visit 4).

| | |
|------------------|---------|
| Arm title | placebo |
|------------------|---------|

Arm description:

placebo

| | |
|--|------------|
| Arm type | Placebo |
| Investigational medicinal product name | placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Buccal use |

Dosage and administration details:

2 / 5 / 10 mini-tablets 0.5-1 hour before bedtime.

| Number of subjects in period 2 | Experimental | placebo |
|---------------------------------------|--------------|---------|
| Started | 60 | 65 |
| Completed | 51 | 44 |
| Not completed | 9 | 21 |
| Consent withdrawn by subject | 3 | 13 |
| Physician decision | 1 | 1 |
| Adverse event, non-fatal | 1 | - |
| other | - | 2 |
| Lost to follow-up | 2 | 5 |
| Protocol deviation | 2 | - |

Period 3

| | |
|------------------------------|-----------------------------|
| Period 3 title | open-label |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------|--------------|
| Arm title | experimental |
|------------------|--------------|

Arm description:

prolonged release melatonin 2, 5 or 10 mg

| | |
|--|-----------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | prolonged release melatonin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Buccal use |

Dosage and administration details:

2 or 5 or 10 mg of prolonged release melatonin pediatric formulation; 0.5-1 hour before bed-time ;

| | |
|--|-----------------------------|
| Investigational medicinal product name | prolonged release melatonin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Buccal use |

Dosage and administration details:

2 or 5 or 10 mg of prolonged release melatonin pediatric formulation; 0.5-1 hour before bed-time ;

| | |
|---------------------------------------|--------------|
| Number of subjects in period 3 | experimental |
| Started | 95 |
| Completed | 74 |
| Not completed | 21 |
| consent withdrawn by parents | 9 |
| Consent withdrawn by subject | 3 |
| Physician decision | 2 |
| Adverse event, non-fatal | 3 |
| other | 1 |
| Lost to follow-up | 1 |
| Protocol deviation | 2 |

Period 4

| | |
|------------------------------|-----------------------------|
| Period 4 title | single-blind run-out |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Single blind |
| Roles blinded | Subject |

Arms

| | |
|------------------|---------|
| Arm title | placebo |
|------------------|---------|

Arm description:

placebo run-out

| | |
|--|------------|
| Arm type | Placebo |
| Investigational medicinal product name | placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Buccal use |

Dosage and administration details:

two, five or ten mini-tablets buccal use 0.5-1 hour before bedtime for two weeks of the period

| | |
|---------------------------------------|---------|
| Number of subjects in period 4 | placebo |
| Started | 74 |
| Completed | 73 |
| Not completed | 1 |
| Lost to follow-up | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------------|
| Reporting group title | placebo run-in |
|-----------------------|----------------|

Reporting group description: -

| Reporting group values | placebo run-in | Total | |
|---------------------------|----------------|-------|--|
| Number of subjects | 267 | 267 | |
| Age categorical | | | |
| Age 2 -18 years old | | | |
| Units: Subjects | | | |
| Children (2-11 years) | 174 | 174 | |
| Adolescents (12-17 years) | 93 | 93 | |
| Age continuous | | | |
| mean age | | | |
| Units: years | | | |
| arithmetic mean | 8.6 | | |
| standard deviation | ± 4.12 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 71 | 71 | |
| Male | 196 | 196 | |

Subject analysis sets

| | |
|----------------------------|-----|
| Subject analysis set title | FAS |
|----------------------------|-----|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

All patients in the Safety Analysis Set who satisfied all major entry criteria (Inclusion Criteria 1-5) and who had a valid mean TST result recorded for baseline and at least one post-baseline period assessment during the double blind phase.

Patients were classified according to randomized treatment. This analysis set was used for all efficacy analyses

| Reporting group values | FAS | | |
|---------------------------|--------|--|--|
| Number of subjects | 119 | | |
| Age categorical | | | |
| Age 2 -18 years old | | | |
| Units: Subjects | | | |
| Children (2-11 years) | 78 | | |
| Adolescents (12-17 years) | 41 | | |
| Age continuous | | | |
| mean age | | | |
| Units: years | | | |
| arithmetic mean | 8.7 | | |
| standard deviation | ± 4.15 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 30 | | |

| | | | |
|------|----|--|--|
| Male | 89 | | |
|------|----|--|--|

| |
|--|
| |
| |

End points

End points reporting groups

| | |
|--|---------------|
| Reporting group title | placebo |
| Reporting group description: single blind | |
| Reporting group title | Experimental |
| Reporting group description: Experimental product - 2 mg or 5 mg | |
| Reporting group title | placebo |
| Reporting group description: placebo | |
| Reporting group title | experimental |
| Reporting group description: prolonged release melatonin 2, 5 or 10 mg | |
| Reporting group title | placebo |
| Reporting group description: placebo run-out | |
| Subject analysis set title | FAS |
| Subject analysis set type | Full analysis |
| Subject analysis set description: All patients in the Safety Analysis Set who satisfied all major entry criteria (Inclusion Criteria 1-5) and who had a valid mean TST result recorded for baseline and at least one post-baseline period assessment during the double blind phase. Patients were classified according to randomized treatment. This analysis set was used for all efficacy analyses | |

Primary: total sleep time

| | |
|---|------------------|
| End point title | total sleep time |
| End point description: <ul style="list-style-type: none">To compare the treatment effect of Circadin® 2/5 mg minitablets to that of placebo on total sleep time (TST) as assessed by the Sleep and Nap Diary after 13 weeks of double-blind treatment | |
| End point type | Primary |
| End point timeframe: 13 weeks | |

| End point values | Experimental | placebo | | |
|----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 58 | 61 | | |
| Units: minutes | | | | |
| arithmetic mean (standard error) | 51.03 (± 10.46) | 18.71 (± 10.82) | | |

| | |
|-----------------------------------|---|
| Attachments (see zip file) | Total Sleep Time/Figure 2Change from baseline in mean total |
|-----------------------------------|---|

Statistical analyses

| | |
|---|--------------------------------|
| Statistical analysis title | MMRM |
| Comparison groups | Experimental v placebo |
| Number of subjects included in analysis | 119 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| Variability estimate | Standard error of the mean |

| | |
|--|--------------------------------|
| Statistical analysis title | MMRM |
| Statistical analysis description: mixed-effects model for repeated-measures | |
| Comparison groups | Experimental v placebo |
| Number of subjects included in analysis | 119 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.035 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 32.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.38 |
| upper limit | 62.26 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 15.1 |

Secondary: Sleep Latency

| | |
|--|---------------|
| End point title | Sleep Latency |
| End point description: <ul style="list-style-type: none">To compare the treatment effect of Circadin® 2/5 mg minitabets to that of placebo on sleep latency as derived from a Sleep and Nap Diary after 13 weeks of double-blind treatment | |
| End point type | Secondary |
| End point timeframe: 13 weeks | |

| End point values | Experimental | placebo | | |
|----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 58 | 61 | | |
| Units: minutes | | | | |
| arithmetic mean (standard error) | -37.77 (\pm 6.816) | -12.57 (\pm 7.005) | | |

| | |
|-----------------------------------|--|
| Attachments (see zip file) | Sleep Latency/Figure 3Change from baseline in mean sleep |
|-----------------------------------|--|

Statistical analyses

| | |
|--|--------------------------------|
| Statistical analysis title | MMRM |
| Statistical analysis description: mixed-effects model for repeated-measures | |
| Comparison groups | Experimental v placebo |
| Number of subjects included in analysis | 119 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.011 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -25.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -44.61 |
| upper limit | -5.8 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 9.787 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

104 weeks

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

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 18 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | placebo DB |
|-----------------------|------------|

Reporting group description:

adverse events during the double blind period on placebo 13 weeks

| | |
|-----------------------|--------------------------------|
| Reporting group title | prolonged release melatonin OL |
|-----------------------|--------------------------------|

Reporting group description:

Prolonged release melatonin during the open label period 91 weeks

| | |
|-----------------------|--------------------------------|
| Reporting group title | prolonged release melatonin DB |
|-----------------------|--------------------------------|

Reporting group description:

prolonged release melatonin double blind period 13 weeks

| Serious adverse events | placebo DB | prolonged release melatonin OL | prolonged release melatonin DB |
|---|----------------|--------------------------------|--------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | 6 / 95 (6.32%) | 0 / 60 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| CONSTIPATION | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 95 (1.05%) | 0 / 60 (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 |
| Psychiatric disorders | | | |
| AGGRESSION | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 95 (1.05%) | 0 / 60 (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 |
| OPPOSITIONAL DEFIANT DISORDER | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 95 (1.05%) | 0 / 60 (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 |

| | | | |
|---|----------------|----------------|----------------|
| Abnormal behaviour | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 95 (1.05%) | 0 / 60 (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 |
| Infections and infestations | | | |
| PNEUMONIA | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | 0 / 95 (0.00%) | 0 / 60 (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 |
| RESPIRATORY TRACT INFECTION VIRAL | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | 0 / 95 (0.00%) | 0 / 60 (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 |
| EYE INFECTION | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 95 (1.05%) | 0 / 60 (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 |
| OTITIS MEDIA ACUTE | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 95 (1.05%) | 0 / 60 (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 |

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

| Non-serious adverse events | placebo DB | prolonged release melatonin OL | prolonged release melatonin DB |
|---|------------------|--------------------------------|--------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 50 / 65 (76.92%) | 80 / 95 (84.21%) | 51 / 60 (85.00%) |
| Nervous system disorders | | | |
| SOMNOLENCE | | | |
| subjects affected / exposed | 8 / 65 (12.31%) | 24 / 95 (25.26%) | 17 / 60 (28.33%) |
| occurrences (all) | 8 | 31 | 18 |
| HEADACHE | | | |
| subjects affected / exposed | 4 / 65 (6.15%) | 12 / 95 (12.63%) | 8 / 60 (13.33%) |
| occurrences (all) | 4 | 12 | 8 |

| | | | |
|---|---|---|--|
| DIZZINESS subjects affected / exposed occurrences (all) | 0 / 65 (0.00%) 0 | 6 / 95 (6.32%) 8 | 0 / 60 (0.00%) 0 |
| General disorders and administration site conditions FATIGUE subjects affected / exposed occurrences (all) PYREXIA subjects affected / exposed occurrences (all) HANGOVER subjects affected / exposed occurrences (all) | 12 / 65 (18.46%) 13 4 / 65 (6.15%) 4 3 / 65 (4.62%) 4 | 25 / 95 (26.32%) 33 7 / 95 (7.37%) 8 7 / 95 (7.37%) 8 | 15 / 60 (25.00%) 19 5 / 60 (8.33%) 5 3 / 60 (5.00%) 4 |
| Gastrointestinal disorders VOMITING subjects affected / exposed occurrences (all) DIARRHOEA subjects affected / exposed occurrences (all) NAUSEA subjects affected / exposed occurrences (all) CONSTIPATION subjects affected / exposed occurrences (all) | 10 / 65 (15.38%) 10 3 / 65 (4.62%) 4 1 / 65 (1.54%) 1 1 / 65 (1.54%) 1 | 20 / 95 (21.05%) 33 3 / 95 (3.16%) 3 9 / 95 (9.47%) 11 8 / 95 (8.42%) 11 | 8 / 60 (13.33%) 11 3 / 60 (5.00%) 3 4 / 60 (6.67%) 4 3 / 60 (5.00%) 4 |
| Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all) DYSPNOEA subjects affected / exposed occurrences (all) ASTHMA subjects affected / exposed occurrences (all) | 5 / 65 (7.69%) 5 4 / 65 (6.15%) 4 1 / 65 (1.54%) 1 | 16 / 95 (16.84%) 27 10 / 95 (10.53%) 10 6 / 95 (6.32%) 8 | 7 / 60 (11.67%) 7 6 / 60 (10.00%) 6 1 / 60 (1.67%) 1 |

| | | | |
|---|------------------------|------------------------|------------------------|
| RHINORRHOEA subjects affected / exposed occurrences (all) | 0 / 65 (0.00%) 0 | 5 / 95 (5.26%) 5 | 2 / 60 (3.33%) 2 |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 3 / 65 (4.62%) 3 | 10 / 95 (10.53%) 10 | 3 / 60 (5.00%) 3 |
| Psychiatric disorders MOOD SWINGS subjects affected / exposed occurrences (all) | 11 / 65 (16.92%) 12 | 17 / 95 (17.89%) 24 | 10 / 60 (16.67%) 10 |
| AGITATION subjects affected / exposed occurrences (all) | 7 / 65 (10.77%) 8 | 8 / 95 (8.42%) 10 | 11 / 60 (18.33%) 12 |
| ANXIETY subjects affected / exposed occurrences (all) | 0 / 65 (0.00%) 0 | 6 / 95 (6.32%) 8 | 0 / 60 (0.00%) 0 |
| AGGRESSION subjects affected / exposed occurrences (all) | 0 / 65 (0.00%) 0 | 5 / 95 (5.26%) 5 | 0 / 60 (0.00%) 0 |
| Infections and infestations UPPER RESPIRATORY TRACT INFECTION subjects affected / exposed occurrences (all) | 7 / 65 (10.77%) 8 | 14 / 95 (14.74%) 24 | 9 / 60 (15.00%) 9 |
| INFLUENZA subjects affected / exposed occurrences (all) | 0 / 65 (0.00%) 0 | 8 / 95 (8.42%) 8 | 0 / 60 (0.00%) 0 |
| OTITIS MEDIA subjects affected / exposed occurrences (all) | 0 / 65 (0.00%) 0 | 7 / 95 (7.37%) 8 | 0 / 60 (0.00%) 0 |
| GASTROENTERITIS subjects affected / exposed occurrences (all) | 0 / 65 (0.00%) 0 | 6 / 95 (6.32%) 8 | 0 / 60 (0.00%) 0 |
| NASOPHARYNGITIS subjects affected / exposed occurrences (all) | 0 / 65 (0.00%) 0 | 6 / 95 (6.32%) 8 | 0 / 60 (0.00%) 0 |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| SINUSITIS | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 5 / 95 (5.26%) | 0 / 60 (0.00%) |
| occurrences (all) | 0 | 5 | 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

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29096777>

<http://www.ncbi.nlm.nih.gov/pubmed/30132686>