



Clinical trial results:

A randomized open-label, multinational, multicentre, phase III clinical study to evaluate the efficacy and safety of Ibuprofen oral suspension 20 mg/ml and Ibuprofen oral suspension 40 mg/ml (Berlin-Chemie) compared with Nurofen® oral suspension 20 mg/ml (Reckitt Benckiser) in children 3-9 years old with uncomplicated acute otitis media

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-004077-32 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 06 June 2014 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 07 September 2016 |
| First version publication date | 07 September 2016 |

Trial information

Trial identification

| | |
|-----------------------|---------------------|
| Sponsor protocol code | BCRU/11/Ibu-AOM/001 |
|-----------------------|---------------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Berlin-Chemie AG |
| Sponsor organisation address | Glienicker Weg 125, Berlin, Germany, 12489 |
| Public contact | Gabriela Drohm, Berlin-Chemie AG, 49 03067072287, GDrohm@berlin-chemie.de |
| Scientific contact | Gabriela Drohm, Berlin-Chemie AG, 49 03067072287, GDrohm@berlin-chemie.de |

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? | Yes |

Notes:

Results analysis stage

| | |
|--|----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 25 August 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 23 May 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 June 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

1. To investigate the analgesic effect of the study drugs Ibuprofen oral suspension 20 mg/ml and Ibuprofen oral suspension 40 mg/ml (ear pain relief assessed by Pain rating scale) in children with AOM.
2. To investigate the antipyretic effect of the study drugs Ibuprofen oral suspension 20 mg/ml and Ibuprofen oral suspension 40 mg/ml (reduction of axillary temperature) in children with AOM.
3. To investigate the anti-inflammatory effect of the study drugs Ibuprofen oral suspension 20 mg/ml and Ibuprofen oral suspension 40 mg/ml (reduction of laboratory markers of inflammation) in children with AOM.
4. To examine the effect of the study drugs Ibuprofen oral suspension 20 mg/ml and Ibuprofen oral suspension 40 mg/ml on appetite, sleep, and playing activity in children with AOM.
5. To evaluate the safety of the study drugs Ibuprofen oral suspension 20 mg/ml and Ibuprofen oral suspension 40 mg/ml based on frequency and severity of treatment-related adverse events.

Protection of trial subjects:

1) Ear pain self-estimation by pain rating scale

Pain estimation was performed at screening, from Day 1 to Day 5 (daily) using the Wong-Baker FACESTM validated 6-item Pain Rating Scale for use in children 3-4 years and older. This scale shows a close linear relationship with the 10-score Visual Analogue Scale. Ear pain intensity was assessed in children as self-report, parents and children were educated in the use of this pain rating scale. On the Visit 2 (Day 3) and Visit 3 (Day 5) pain estimation was performed under the investigator's control, on all other days the pain estimation was performed by the subject and registered by subject's parents in the Parent's Diary.

2) Estimation of quality of life improvement

Estimation of patients' quality of life was performed using a custom non-validated scale, consisting of three items: appetite, sleep, and playing activity (scores 0 – severe impairment, 1 – mild impairment, 2 – normal) once daily in the morning, on each day of the analgesic treatment period (Days 1 to 5) compared to baseline (Visit 1, Day 1). Quality of life was assessed by subject's parents, and the investigator only recorded the result of the estimation directly in the CRF during visits.

Background therapy:

Below detailed obligatory concomitant medication, amoxicillin, was used across all arm/groups in the trial

Name: Flemoxin Solutab (INN – amoxicillin), Astellas Pharma Europe B.V., Netherlands.

Pharmacokinetic group: antibiotic, semisynthetic penicilline.

Pharmaceutical form: orodispersible tablets. Each tablet contains amoxicillin as the trihydrate 125 or 250 mg;

Dose and route of administration: Flemoxin Solutab was administered according to the Prescribing Information: the recommended daily dosage of amoxicillin in mild and moderate infections is 375 mg in children 1-3 years, and 750 mg in children 4-10 years, or 30-60 mg/kg per day (twice or thrice daily).

Evidence for comparator:

Name: Nurofen® oral suspension 20 mg/ml (INN - ibuprofen), Reckitt Benckiser, UK.

Pharmacokinetic group: non-steroidal anti-inflammatory drug.

Dose and route of administration: 3-4 per day/100-600 mg (oral)

| | |
|---|---------------|
| Actual start date of recruitment | 24 April 2013 |
| 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 | Ukraine: 48 |
| Country: Number of subjects enrolled | Russian Federation: 87 |
| Worldwide total number of subjects | 135 |
| EEA total number of subjects | 0 |

Notes:

Subjects enrolled per age group

| | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 135 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Ukraine

date of first subject enrollment: 24/APR/2013

date of last subject completed: 24/MAR/2014

Russia

date of first subject enrollment: 19/FEB/2014

date of last subject completed: 23/MAY/2014

Pre-assignment

Screening details:

At screening (Day 1) the physical examination, measurement of blood pressure (BP), heart rate and blood analyses (haematology, biochemistry) was done. Immediately after screening suitable subjects were randomised.

Pre-assignment period milestones

| | |
|------------------------------|-----|
| Number of subjects started | 135 |
| Number of subjects completed | 135 |

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Test drug low dose |

Arm description: -

| | |
|--|------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ibuprofen oral suspension 20 mg/ml |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

administered to all patients in this group from Day 1 (5-10 mg/kg BW, 3-4 times daily, maximum dosage 30 mg/kg BW daily) with the duration of administration of 3-5 days.

| | |
|------------------|---------------------|
| Arm title | Test drug high dose |
|------------------|---------------------|

Arm description: -

| | |
|--|------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ibuprofen oral suspension 40 mg/ml |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

administered to all patients in this group from Day 1 (5-10 mg/kg BW, 3-4 times daily, maximum

dosage 30 mg/kg BW daily) with the duration of administration of 3-5 days.

| | |
|--|---|
| Arm title | comparator drug |
| Arm description: - | |
| Arm type | Active comparator |
| Investigational medicinal product name | Nurofen® oral suspension 20 mg/ml (Reckitt Benckiser, UK) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

administered to all patients in this group from Day 1 (5-10 mg/kg BW, 3-4 times daily, maximum dosage 30 mg/kg BW daily) with a duration of administration of 3-5 days.

| Number of subjects in period 1 | Test drug low dose | Test drug high dose | comparator drug |
|---------------------------------------|--------------------|---------------------|-----------------|
| Started | 46 | 45 | 44 |
| Completed | 46 | 45 | 44 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|---------------------|
| Reporting group title | Test drug low dose |
| Reporting group description: - | |
| Reporting group title | Test drug high dose |
| Reporting group description: - | |
| Reporting group title | comparator drug |
| Reporting group description: - | |

| Reporting group values | Test drug low dose | Test drug high dose | comparator drug |
|---------------------------------------|--------------------|---------------------|-----------------|
| Number of subjects | 46 | 45 | 44 |
| Age categorical Units: Subjects | | | |
| Children 3-9 years old | 46 | 45 | 44 |
| Gender categorical Units: Subjects | | | |
| Female | 20 | 17 | 20 |
| Male | 26 | 28 | 24 |

| Reporting group values | Total | | |
|---------------------------------------|-------|--|--|
| Number of subjects | 135 | | |
| Age categorical Units: Subjects | | | |
| Children 3-9 years old | 135 | | |
| Gender categorical Units: Subjects | | | |
| Female | 57 | | |
| Male | 78 | | |

End points

End points reporting groups

| | |
|--------------------------------|---------------------|
| Reporting group title | Test drug low dose |
| Reporting group description: - | |
| Reporting group title | Test drug high dose |
| Reporting group description: - | |
| Reporting group title | comparator drug |
| Reporting group description: - | |

Primary: Pain relief

| | |
|---|-------------|
| End point title | Pain relief |
| End point description: proportions of patients with pain relief, defined as a reduction of pain score by ≥ 2 on the 6-item Wong-Baker FACES Pain Rating Scale | |
| End point type | Primary |
| End point timeframe: at 48 hours (Day 3) of therapy | |

| End point values | Test drug low dose | Test drug high dose | comparator drug | |
|----------------------------------|------------------------|---------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 44 | 43 | 43 | |
| Units: pain | | | | |
| number (confidence interval 95%) | 97.73 (87.98 to 99.94) | 100 (91.78 to 100) | 97.67 (87.71 to 99.94) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Analysis of efficacy |
| Statistical analysis description: The null hypothesis was non-inferiority of each test drug versus active control using Fisher's exact test. The one -sided significance level was 0.025% with a power of 80% and a non-inferiority margin of -15% . Since there were 3 groups, in order to avoid a statistical type I error adjustment according to Bonferroni was performed. | |
| Comparison groups | Test drug low dose v Test drug high dose v comparator drug |
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[1] |
| P-value | ≤ 0.05 ^[2] |
| Method | Fisher exact |

| Confidence interval | |
|---------------------|---------|
| level | 95 % |
| sides | 2-sided |

Notes:

[1] - Statistical analysis of primary endpoint is presented as absolute number and frequency (%) of patients with ear pain relief (defined as reduction of pain score by ≥ 2) or no pain relief (no reduction of pain score by ≥ 2), at Day 3 (Visit 2). The children have been evaluated as having met the criteria for either clinical response (ear pain relief) or clinical failure (presence of pain).

[2] - P-values and confidence intervals will be 2-sided, and statistical significance will be declared at the 2-sided 0.05-level, unless otherwise specified (when rounded to three decimal places).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

At Visit 1 (Screening, Day 1) and each visit to the study center during the study.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 15.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Group 1 |
|-----------------------|---------|

Reporting group description:

Ibuprofen 20mg/ml

| | |
|-----------------------|---------|
| Reporting group title | Group 2 |
|-----------------------|---------|

Reporting group description:

Ibuprofen 40 mg/ml

| | |
|-----------------------|---------|
| Reporting group title | Group 3 |
|-----------------------|---------|

Reporting group description:

Nurofen 20 mg/ml

| Serious adverse events | Group 1 | Group 2 | Group 3 |
|---|----------------|----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 45 (0.00%) | 0 / 44 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

Frequency threshold for reporting non-serious adverse events: 4 %

| Non-serious adverse events | Group 1 | Group 2 | Group 3 |
|---|------------------|----------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 10 / 46 (21.74%) | 4 / 45 (8.89%) | 10 / 44 (22.73%) |
| Investigations | | | |
| Body temperature increased | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 45 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 0 | 1 |
| Vascular disorders | | | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 45 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|--|----------------|----------------|----------------|
| Nervous system disorders | | | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 45 (2.22%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 1 | 1 |
| Headache | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 45 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Hypothermia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 1 / 45 (2.22%) | 0 / 44 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hyperthermia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 45 (0.00%) | 2 / 44 (4.55%) |
| occurrences (all) | 0 | 0 | 2 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 45 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 1 / 45 (2.22%) | 2 / 44 (4.55%) |
| occurrences (all) | 1 | 1 | 2 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 0 / 45 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 0 | 1 |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 46 (8.70%) | 1 / 45 (2.22%) | 1 / 44 (2.27%) |
| occurrences (all) | 4 | 1 | 1 |
| Nausea | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 45 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 1 | 0 | 1 |
| Aphthous stomatitis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 45 (2.22%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Tracheitis | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | 0 / 45 (0.00%) 0 | 0 / 44 (0.00%) 0 |
| Rhinitis subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | 0 / 45 (0.00%) 0 | 0 / 44 (0.00%) 0 |
| acute tonsillitis subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 1 / 45 (2.22%) 1 | 0 / 44 (0.00%) 0 |
| Skin and subcutaneous tissue disorders | | | |
| Erythema subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | 0 / 45 (0.00%) 0 | 0 / 44 (0.00%) 0 |
| Rash subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | 1 / 45 (2.22%) 1 | 0 / 44 (0.00%) 0 |
| Infections and infestations | | | |
| Otitis media subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | 0 / 45 (0.00%) 0 | 0 / 44 (0.00%) 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 27 November 2012 | <p>Protocol amendment Version 2.0 was developed in order to implement a more precise estimation of the sample size with the following sample size increase and to specify some statistical issues. The randomization procedure for the investigator was also adapted to a more appropriate and convenient method in this open-label trial. Changes were made in the following sections of the protocol:</p> <ul style="list-style-type: none">– In section "Randomization", to simplify the randomization procedure – previously designated numbered sealed envelopes with randomization numbers were replaced with the drug labeling according to the randomization list and IMP administration in accordance with the randomization number visible on the label of the study medication;– In section "Planned number of patients", to implement the more precise estimation of the sample size – it was recalculated to a new value, with requirement to include in the trial not less than 45 patients per group, 135 in total, instead of not less than 35 patients per group, overall 105 patients in the previous version of the protocol.– In section "The level of significance to be used" – information about efficacy endpoints methods of statistical analysis and overall probability of type I was added. |
| 25 September 2013 | <p>Protocol amendment Version 3.0 was developed in order to introduce new facts established in the course of conduction of preclinical investigation of acute and sub-chronic toxicity of the study drug. Changes were made in the "Non-clinical and clinical data" section of the protocol – updated information about acute and sub-chronic toxicity pre-clinical studies was added.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported