



## 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
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#### 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
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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:

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**Results analysis stage**

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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:

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**General information about the trial**

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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 FACES<sup>TM</sup> 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.

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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).

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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
<b>Arm title</b>	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.

<b>Arm title</b>	Test drug high dose
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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.

<b>Arm title</b>	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.

<b>Number of subjects in period 1</b>	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 $\geq 2$ 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 <sup>[1]</sup>
P-value	$\leq 0.05$ <sup>[2]</sup>
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  $\geq 2$ ) or no pain relief (no reduction of pain score by  $\geq 2$ ), 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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.1
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### Reporting groups

Reporting group title	Group 1
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Reporting group description:

Ibuprofen 20mg/ml

Reporting group title	Group 2
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Reporting group description:

Ibuprofen 40 mg/ml

Reporting group title	Group 3
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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"><li>– 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;</li><li>– 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.</li><li>– 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.</li></ul>
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:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported