



## Clinical trial results:

### Multicenter, Double-Blind, Randomized, Parallel, Placebo-Controlled Trial Assessing the Analgesic Efficacy of a Single, Oral Dose of an Extended Release Naproxen Sodium Tablet in Postsurgical Dental Pain Summary

EudraCT number	2014-005269-66
Trial protocol	Outside EU/EEA
Global end of trial date	29 August 2008

#### Results information

Result version number	v1
This version publication date	12 July 2016
First version publication date	15 July 2015

#### Trial information

##### Trial identification

Sponsor protocol code	BAY117031/13130
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00720057
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Bayer HealthCare AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, D-51368, Germany,
Public contact	Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.com
Scientific contact	Therapeutic Area Head, Bayer HealthCare AG, clinical-trials-contact@bayerhealthcare.com

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 September 2008
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	29 August 2008
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the analgesic efficacy of a single, oral dose of a naproxen sodium extended-release (ER) tablet, compared to placebo in postsurgical dental pain.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects and/or their legally authorized representative. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 June 2008
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	United States: 312
Worldwide total number of subjects	312
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)	0
Adolescents (12-17 years)	65
Adults (18-64 years)	247

From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Three sites in the United States enrolled subjects in the trial between 27 June 2008 (date of first enrollment) and 02 September 2008 (date of last contact).

### Pre-assignment

Screening details:

The screening period occurred up to 28 days prior to the day of dental surgery. A total of 447 subjects were screened, of which 135 were excluded (72 did not meet inclusion criteria, 19 refused to participate, 44 other reasons); 312 subjects were randomized and included in the intent-to-treat (ITT) population for efficacy and safety analysis.

### Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Naproxen Sodium ER (BAYH6689)

Arm description:

Single dose (1 tablet) ER Naproxen sodium 660 milligram (mg) with a full glass of water (240 milliliter [mL]) within 1-4 hours post dental surgery.

Arm type	Experimental
Investigational medicinal product name	Naproxen Sodium Extended Release Tablet
Investigational medicinal product code	BAYH6689
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Single dose (1 tablet) ER Naproxen sodium 660 mg with a full glass of water (240 mL) within 1-4 hours post dental surgery.

<b>Arm title</b>	Placebo
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Arm description:

Single dose (1 tablet) of placebo with a full glass of water (240 mL) within 1-4 hours post dental surgery.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Single dose (1 tablet) of placebo with a full glass of water (240 mL) within 1-4 hours post dental surgery.

<b>Number of subjects in period 1</b>	<b>Naproxen Sodium ER (BAYH6689)</b>	<b>Placebo</b>
Started	153	159
Completed	152	156
Not completed	1	3
Consent withdrawn by subject	-	1
Protocol violation	1	-
Lost to follow-up	-	2

## Baseline characteristics

### Reporting groups

Reporting group title	Naproxen Sodium ER (BAYH6689)
Reporting group description: Single dose (1 tablet) ER Naproxen sodium 660 milligram (mg) with a full glass of water (240 milliliter [mL]) within 1-4 hours post dental surgery.	
Reporting group title	Placebo
Reporting group description: Single dose (1 tablet) of placebo with a full glass of water (240 mL) within 1-4 hours post dental surgery.	

Reporting group values	Naproxen Sodium ER (BAYH6689)	Placebo	Total
Number of subjects	153	159	312
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	20.8 ± 4.03	20.4 ± 4.31	-
Gender categorical Units: Subjects			
Female	89	106	195
Male	64	53	117
Baseline Pain Intensity by Categorical Scale			
Categorical scale: No Pain (0), Mild Pain (1), Moderate Pain (2), Severe Pain (3).			
Units: Subjects			
Moderate	99	103	202
Severe	54	56	110
Baseline Pain Intensity by Visual Analog Scale			
Visual Analog Scale 0-100 millimeter (mm): 0=no pain and 100=worse possible pain.			
Units: scores on a scale arithmetic mean standard deviation	72.3 ± 13.13	72.6 ± 11.91	-

## End points

### End points reporting groups

Reporting group title	Naproxen Sodium ER (BAYH6689)
Reporting group description: Single dose (1 tablet) ER Naproxen sodium 660 milligram (mg) with a full glass of water (240 milliliter [mL]) within 1-4 hours post dental surgery.	
Reporting group title	Placebo
Reporting group description: Single dose (1 tablet) of placebo with a full glass of water (240 mL) within 1-4 hours post dental surgery.	
Subject analysis set title	Intent-to-Treat (ITT) population
Subject analysis set type	Intention-to-treat
Subject analysis set description: Randomized population was defined as all subjects who signed informed consent form, completed the screening period, and were randomized. The ITT population was defined as all subjects who were randomized and received at least one dose of the study treatment. Efficacy analyses were based on the ITT population (n=312).	

### Primary: Summed Pain Intensity Difference (SPID)

End point title	Summed Pain Intensity Difference (SPID)
End point description: Categorical pain intensity scale - no pain (0), mild pain (1), moderate pain (2), or severe pain (3) was used for all pain intensity assessments postdose. Time-weighted SPID was calculated by multiplying the Pain Intensity Difference (PID) score at each postdose time point by the duration (in hours) since the preceding time point and then summing these values over 0-24 and 16-24 hours, respectively.	
End point type	Primary
End point timeframe: 0 to 24 hours post dose	

End point values	Naproxen Sodium ER (BAYH6689)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153 <sup>[1]</sup>	159 <sup>[2]</sup>		
Units: units on a scale				
arithmetic mean (standard deviation)				
SPID 0-24	25.9 (± 25.87)	-3.1 (± 18.4)		
SPID 16-24	8.8 (± 9.3)	-1 (± 6.89)		

Notes:

[1] - ITT population.

[2] - ITT population.

### Statistical analyses

Statistical analysis title	Summed Pain Intensity Difference (SPID)
Statistical analysis description: The treatment differences between the two groups were tested each at the 5% two-sided significant level using a hierarchical testing procedure to control the overall type 1 error. SPID16-24 was eligible for testing only after a statistically significant difference between the two arms with respect to SPID0-24 was observed. The SPIDs were analyzed via Analysis of Co-variance (ANCOVA) model with treatment and trial site as fixed effects and baseline pain intensity score as the covariate.	

Comparison groups	Naproxen Sodium ER (BAYH6689) v Placebo
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	other <sup>[3]</sup>
P-value	< 0.001
Method	ANCOVA

Notes:

[3] - Placebo-controlled

### Secondary: Total Pain Relief (TOTPAR)

End point title	Total Pain Relief (TOTPAR)
End point description:	
Pain relief categorical rating scale - no relief (0), a little relief (1), some relief (2), a lot of relief (3), or complete relief (4) was used for all pain relief assessments postdose. TOTPAR was calculated by multiplying the pain relief score at each postdose time point by the duration (in hours) since the preceding time point and then summing these values.	
End point type	Secondary
End point timeframe:	
0-24 hours post dose	

End point values	Naproxen Sodium ER (BAYH6689)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153 <sup>[4]</sup>	159 <sup>[5]</sup>		
Units: units on a scale				
arithmetic mean (standard deviation)				
TOTPAR 0 - 6 hours	12.7 (± 7.81)	3.1 (± 5.07)		
TOTPAR 0 - 12 hours	25.5 (± 17.06)	5.5 (± 10.7)		
TOTPAR 0 - 16 hours	34.1 (± 23.49)	7.2 (± 14.83)		
TOTPAR 0 - 24 hours	51.3 (± 36.41)	10.9 (± 23.95)		
TOTPAR 16 - 24 hours	17.2 (± 13.37)	3.7 (± 9.4)		

Notes:

[4] - ITT population.

[5] - ITT population.

### Statistical analyses

Statistical analysis title	Total Pain Relief (TOTPAR)
Comparison groups	Naproxen Sodium ER (BAYH6689) v Placebo
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	other <sup>[6]</sup>
P-value	< 0.001
Method	ANCOVA

Notes:

[6] - Placebo-controlled

### Secondary: Summed Pain Intensity Difference at Specific Time Intervals



End point title	Summed Pain Intensity Difference at Specific Time Intervals
End point description:	
Categorical pain intensity scale - no pain (0), mild pain (1), moderate pain (2), or severe pain (3) was used for all pain intensity assessments postdose. Time-weighted SPID was calculated by multiplying the PID score at each postdose time point by the duration (in hours) since the preceding time point and then summing these values for 0-6, 0-12, 0-16 hour intervals, respectively.	
End point type	Secondary
End point timeframe:	
0-16 hours post dose	

End point values	Naproxen Sodium ER (BAYH6689)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153 <sup>[7]</sup>	159 <sup>[8]</sup>		
Units: units on a scale				
arithmetic mean (standard deviation)				
SPID 0 - 6	6.2 (± 5.7)	-0.4 (± 4.2)		
SPID 0 - 12	12.7 (± 12.3)	-1.4 (± 8.54)		
SPID 0 - 16	17.1 (± 16.85)	-2 (± 11.68)		

Notes:

[7] - ITT population.

[8] - ITT population.

## Statistical analyses

Statistical analysis title	SPID at Specific Time Intervals
Comparison groups	Naproxen Sodium ER (BAYH6689) v Placebo
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	other <sup>[9]</sup>
P-value	< 0.001
Method	ANCOVA

Notes:

[9] - Placebo-controlled

## Secondary: Time to First Use of Rescue Medication

End point title	Time to First Use of Rescue Medication
End point description:	
Time to first use of rescue medication was estimated using the Kaplan-Meier method and analyzed by a log rank test stratified by trial site and baseline pain intensity (PI). The endpoint was time to first use of rescue medication. The criteria were if adequate pain relief was not achieved, then subjects were permitted to take rescue medication.	
End point type	Secondary
End point timeframe:	
Post dose to first use of rescue medication	

End point values	Naproxen Sodium ER (BAYH6689)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153 <sup>[10]</sup>	159 <sup>[11]</sup>		
Units: hours				
median (full range (min-max))	22.27 (1.07 to 22.27)	1.9 (1.03 to 10.12)		

Notes:

[10] - ITT population.

[11] - ITT population.

## Statistical analyses

Statistical analysis title	Time to First Use of Rescue Medication
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Statistical analysis description:

The statistics were from the Kaplan-Meier method. The median for naproxen treatment arm was not estimable from Kaplan-Meier method, therefore it was presented as the maximum value from the full range.

Comparison groups	Naproxen Sodium ER (BAYH6689) v Placebo
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	other <sup>[12]</sup>
P-value	< 0.001
Method	Logrank

Notes:

[12] - Placebo-controlled

## Secondary: Global Assessment of the Investigational Product as a Pain Reliever

End point title	Global Assessment of the Investigational Product as a Pain Reliever
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End point description:

Categorical Scale: Poor (0), Fair (1), Good (2), Very Good (3), Excellent (4).

End point type	Secondary
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End point timeframe:

At 24 hours postdose or immediately before first use of rescue medication

End point values	Naproxen Sodium ER (BAYH6689)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153 <sup>[13]</sup>	159 <sup>[14]</sup>		
Units: units on a scale				
arithmetic mean (standard deviation)	2.3 (± 1.43)	0.6 (± 1.04)		

Notes:

[13] - ITT population.

[14] - ITT population.

## Statistical analyses

<b>Statistical analysis title</b>	Global Assessment of the Investigational Product
Comparison groups	Naproxen Sodium ER (BAYH6689) v Placebo
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	other <sup>[15]</sup>
P-value	< 0.001
Method	Cochran-Mantel-Haenszel

Notes:

[15] - Placebo-controlled

## Secondary: Time to Onset of Effect

End point title	Time to Onset of Effect
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End point description:

Time to onset of effect was defined as the time to meaningful pain relief, provided that the subjects experienced both "perceptible" and "meaningful" pain relief. Perceptible pain relief was defined as when the subject first began to feel any pain-relieving effect from the investigational product. Meaningful pain relief was defined as when the subject felt the degree of pain relief was meaningful to them.

End point type	Secondary
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End point timeframe:

From post dose to onset of first perceptible and meaningful pain relief for up to 6 hours

End point values	Naproxen Sodium ER (BAYH6689)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153 <sup>[16]</sup>	159 <sup>[17]</sup>		
Units: hours				
median (full range (min-max))	1.37 (0.07 to 4.98)	4.13 (0.07 to 4.75)		

Notes:

[16] - ITT population.

[17] - ITT population.

## Statistical analyses

<b>Statistical analysis title</b>	Time to Onset of Effect
Comparison groups	Naproxen Sodium ER (BAYH6689) v Placebo
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	other <sup>[18]</sup>
P-value	< 0.001
Method	Logrank

Notes:

[18] - Placebo-controlled

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded throughout the treatment period through 5 days after investigational product or placebo administration. All serious adverse events were collected through about 30 days after the last dose of investigational product or placebo.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	11.0
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### Reporting groups

Reporting group title	Placebo
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Reporting group description:

Single dose (1 tablet) of placebo with a full glass of water (240 mL) within 1-4 hours post dental surgery.

Reporting group title	Naproxen Sodium ER (BAYH6689)
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Reporting group description:

Single dose (1 tablet) ER Naproxen sodium 660 mg with a full glass of water (240 mL) within 1-4 hours post dental surgery.

Serious adverse events	Placebo	Naproxen Sodium ER (BAYH6689)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 159 (0.00%)	0 / 153 (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 %

Non-serious adverse events	Placebo	Naproxen Sodium ER (BAYH6689)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 159 (22.64%)	10 / 153 (6.54%)	
Injury, poisoning and procedural complications			
POST PROCEDURAL HAEMORRHAGE			
subjects affected / exposed	1 / 159 (0.63%)	0 / 153 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
FLUSHING			

subjects affected / exposed occurrences (all)	0 / 159 (0.00%) 0	1 / 153 (0.65%) 1	
Nervous system disorders DIZZINESS subjects affected / exposed occurrences (all)	8 / 159 (5.03%) 8	1 / 153 (0.65%) 1	
HEADACHE subjects affected / exposed occurrences (all)	6 / 159 (3.77%) 6	5 / 153 (3.27%) 5	
SYNCOPE subjects affected / exposed occurrences (all)	1 / 159 (0.63%) 1	1 / 153 (0.65%) 1	
General disorders and administration site conditions PYREXIA subjects affected / exposed occurrences (all)	0 / 159 (0.00%) 0	1 / 153 (0.65%) 1	
Ear and labyrinth disorders TINNITUS subjects affected / exposed occurrences (all)	1 / 159 (0.63%) 1	0 / 153 (0.00%) 0	
Eye disorders CONJUNCTIVITIS subjects affected / exposed occurrences (all)	1 / 159 (0.63%) 2	0 / 153 (0.00%) 0	
EYE SWELLING subjects affected / exposed occurrences (all)	0 / 159 (0.00%) 0	1 / 153 (0.65%) 1	
SCOTOMA subjects affected / exposed occurrences (all)	1 / 159 (0.63%) 1	0 / 153 (0.00%) 0	
Gastrointestinal disorders ABDOMINAL PAIN subjects affected / exposed occurrences (all)	1 / 159 (0.63%) 1	0 / 153 (0.00%) 0	
DYSPEPSIA			

subjects affected / exposed	1 / 159 (0.63%)	0 / 153 (0.00%)	
occurrences (all)	1	0	
NAUSEA			
subjects affected / exposed	24 / 159 (15.09%)	3 / 153 (1.96%)	
occurrences (all)	24	3	
STOMACH DISCOMFORT			
subjects affected / exposed	1 / 159 (0.63%)	0 / 153 (0.00%)	
occurrences (all)	1	0	
TOOTH SOCKET HAEMORRHAGE			
subjects affected / exposed	2 / 159 (1.26%)	1 / 153 (0.65%)	
occurrences (all)	2	1	
VOMITING			
subjects affected / exposed	14 / 159 (8.81%)	2 / 153 (1.31%)	
occurrences (all)	14	2	
Respiratory, thoracic and mediastinal disorders			
PHARYNGOLARYNGEAL PAIN			
subjects affected / exposed	0 / 159 (0.00%)	1 / 153 (0.65%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
HYPERHIDROSIS			
subjects affected / exposed	1 / 159 (0.63%)	0 / 153 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
ABSCCESS ORAL			
subjects affected / exposed	0 / 159 (0.00%)	1 / 153 (0.65%)	
occurrences (all)	0	1	
TOOTH ABSCESS			
subjects affected / exposed	1 / 159 (0.63%)	0 / 153 (0.00%)	
occurrences (all)	1	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 July 2008	To ensure consistency and accuracy of time measurements, the amendment instructed trial coordinators, rather than subjects, to start the stopwatches at the time of dosing.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported