



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 |
|-----------------------|-----------------|

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 | Subject, Investigator |

Arms

| | |
|------------------------------|-------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | 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.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

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.

| Number of subjects in period 1 | Naproxen Sodium ER (BAYH6689) | Placebo |
|---------------------------------------|----------------------------------|---------|
| 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 ^[1] | 159 ^[2] | | |
| 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 ^[3] |
| 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 ^[4] | 159 ^[5] | | |
| 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 ^[6] |
| 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 ^[7] | 159 ^[8] | | |
| 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 ^[9] |
| 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 ^[10] | 159 ^[11] | | |
| 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 |
|----------------------------|--|
|----------------------------|--|

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 ^[12] |
| 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 |
|-----------------|---|

End point description:

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

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

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 ^[13] | 159 ^[14] | | |
| 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

| | |
|---|--|
| Statistical analysis title | 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 ^[15] |
| 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 |
|-----------------|-------------------------|

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 |
|----------------|-----------|

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 ^[16] | 159 ^[17] | | |
| 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

| | |
|---|---|
| Statistical analysis title | 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 ^[18] |
| 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 |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 11.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| 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 title | Naproxen Sodium ER (BAYH6689) |
|-----------------------|-------------------------------|

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

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported