



Clinical trial results:

A Randomized, Double-Blind, Single-Dose, Parallel, Placebo-Controlled Trial to Determine the Dose of Caffeine in a Fixed Dose Combination Tablet of Naproxen Sodium and Caffeine to Effectively Alleviate Postsurgical Dental Pain

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2019-003513-33 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 03 March 2020 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v2 (current) |
| This version publication date | 25 August 2021 |
| First version publication date | 13 September 2020 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|------------------|
| Sponsor protocol code | BAY2880376/21069 |
|-----------------------|------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04132336 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Bayer AG |
| Sponsor organisation address | Kaiser Wilhelm Allee, Leverkusen, Germany, D-51368 |
| Public contact | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com |
| Scientific contact | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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 | 03 March 2020 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|---------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 03 March 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare a single oral dose of the fixed dose combination (FDC) relative to naproxen sodium 220 mg, Caffeine 200 mg and placebo

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. 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 | 12 November 2019 |
| 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: 193 |
| Worldwide total number of subjects | 193 |
| 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) | 91 |
| Adults (18-64 years) | 102 |
| From 65 to 84 years | 0 |

| | |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

Subject disposition

Recruitment

Recruitment details:

Study was conducted at a single center in United States between 12-Nov-2019 (first subject first visit) and 02-Mar-2020 (last subject last visit). Study was completed on 03-Mar-2020 (End of follow up, phone call).

Pre-assignment

Screening details:

A total of 193 subjects, including 32 in each of the naproxen sodium containing groups, 16 in the caffeine group, and 17 in the placebo group, underwent dental surgery and were randomized to study drug.

Period 1

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

Arms

| | |
|------------------------------|---------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Naproxen Sodium/Caffeine-Dose 1 |

Arm description:

Subjects received a single dose of two tablets of naproxen sodium/caffeine (low dose/medium low dose) after extraction of third molars

| | |
|--|--------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Naproxen sodium/Caffeine |
| Investigational medicinal product code | BAY2880376 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Tablet, oral, single dose

| | |
|------------------|---------------------------------|
| Arm title | Naproxen Sodium/Caffeine-Dose 2 |
|------------------|---------------------------------|

Arm description:

Subjects received a single dose of two tablets of naproxen sodium/caffeine (low dose/low dose) after extraction of third molars

| | |
|--|--------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Naproxen sodium/Caffeine |
| Investigational medicinal product code | BAY2880376 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Tablet, oral, single dose

| | |
|------------------|---------------------------------|
| Arm title | Naproxen Sodium/Caffeine-Dose 3 |
|------------------|---------------------------------|

Arm description:

Subjects received a single dose of one tablet of naproxen sodium/caffeine (low dose/ medium low dose) plus one tablet of placebo after extraction of third molars

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|---------------------------------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Tablet, oral, single dose | |
| Investigational medicinal product name | Naproxen sodium/Caffeine |
| Investigational medicinal product code | BAY2880376 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Tablet, oral, single dose | |
| Arm title | Naproxen Sodium/Caffeine-Dose 4 |
| Arm description: | |
| Subjects received a single dose of one tablet of naproxen sodium/caffeine (low dose/ low dose) plus one tablet of placebo after extraction of third molars | |
| Arm type | Experimental |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Tablet, oral, single dose | |
| Investigational medicinal product name | Naproxen sodium/Caffeine |
| Investigational medicinal product code | BAY2880376 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Tablet, oral, single dose | |
| Arm title | Naproxen Sodium |
| Arm description: | |
| Subjects received a single dose of one tablet of naproxen sodium (low dose) plus one tablet of placebo after extraction of third molars | |
| Arm type | Active comparator |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Tablet, oral, single dose | |
| Investigational medicinal product name | Naproxen sodium |
| Investigational medicinal product code | BAY117031 |
| Other name | Aleve |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Tablet, oral, single dose | |

| | |
|---|-------------------|
| Arm title | Caffeine |
| Arm description: Subjects received a single dose of two tablets of caffeine (medium low dose) after extraction of third molars | |
| Arm type | Active comparator |
| Investigational medicinal product name | Caffeine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: Tablet, oral, single dose | |
| Arm title | Placebo |
| Arm description: Subjects received a single dose of two tablets of matching placebo after extraction of third molars | |
| 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: Tablet, oral, single dose | |

| Number of subjects in period 1 | Naproxen Sodium/Caffeine-Dose 1 | Naproxen Sodium/Caffeine-Dose 2 | Naproxen Sodium/Caffeine-Dose 3 |
|---------------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Started | 32 | 32 | 32 |
| Completed | 32 | 31 | 32 |
| Not completed | 0 | 1 | 0 |
| Investigator Decision | - | 1 | - |

| Number of subjects in period 1 | Naproxen Sodium/Caffeine-Dose 4 | Naproxen Sodium | Caffeine |
|---------------------------------------|---------------------------------|-----------------|----------|
| Started | 32 | 32 | 16 |
| Completed | 32 | 32 | 16 |
| Not completed | 0 | 0 | 0 |
| Investigator Decision | - | - | - |

| Number of subjects in period 1 | Placebo |
|---------------------------------------|---------|
| Started | 17 |
| Completed | 17 |
| Not completed | 0 |
| Investigator Decision | - |

Baseline characteristics

Reporting groups

| | |
|---|---------------------------------|
| Reporting group title | Naproxen Sodium/Caffeine-Dose 1 |
| Reporting group description: Subjects received a single dose of two tablets of naproxen sodium/caffeine (low dose/medium low dose) after extraction of third molars | |
| Reporting group title | Naproxen Sodium/Caffeine-Dose 2 |
| Reporting group description: Subjects received a single dose of two tablets of naproxen sodium/caffeine (low dose/low dose) after extraction of third molars | |
| Reporting group title | Naproxen Sodium/Caffeine-Dose 3 |
| Reporting group description: Subjects received a single dose of one tablet of naproxen sodium/caffeine (low dose/ medium low dose) plus one tablet of placebo after extraction of third molars | |
| Reporting group title | Naproxen Sodium/Caffeine-Dose 4 |
| Reporting group description: Subjects received a single dose of one tablet of naproxen sodium/caffeine (low dose/ low dose) plus one tablet of placebo after extraction of third molars | |
| Reporting group title | Naproxen Sodium |
| Reporting group description: Subjects received a single dose of one tablet of naproxen sodium (low dose) plus one tablet of placebo after extraction of third molars | |
| Reporting group title | Caffeine |
| Reporting group description: Subjects received a single dose of two tablets of caffeine (medium low dose) after extraction of third molars | |
| Reporting group title | Placebo |
| Reporting group description: Subjects received a single dose of two tablets of matching placebo after extraction of third molars | |

| Reporting group values | Naproxen Sodium/Caffeine-Dose 1 | Naproxen Sodium/Caffeine-Dose 2 | Naproxen Sodium/Caffeine-Dose 3 |
|------------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Number of subjects | 32 | 32 | 32 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|----------------|----------------|----------------|
| Age continuous Units: years arithmetic mean standard deviation | 17.0 ± 1.03 | 17.4 ± 2.42 | 17.1 ± 1.34 |
| Gender categorical Units: Subjects | | | |
| Female | 13 | 14 | 16 |
| Male | 19 | 18 | 16 |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 2 | 0 | 0 |
| Not Hispanic or Latino | 30 | 32 | 32 |
| Race Units: Subjects | | | |

| | | | |
|---|----|----|----|
| White | 31 | 31 | 30 |
| Black or African American | 0 | 0 | 1 |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 1 | 1 |
| Native Hawaiian or Other Pacific Islander | 1 | 0 | 0 |
| Other | 0 | 0 | 0 |
| Baseline Pain Intensity Score | | | |
| Units: Subjects | | | |
| No Pain (0) | 0 | 0 | 0 |
| Mild Pain (1) | 0 | 0 | 0 |
| Moderate Pain (2) | 15 | 13 | 12 |
| Severe Pain (3) | 17 | 19 | 20 |

| Reporting group values | Naproxen Sodium/Caffeine-Dose 4 | Naproxen Sodium | Caffeine |
|------------------------|---------------------------------|-----------------|----------|
| Number of subjects | 32 | 32 | 16 |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|--------|--------|--------|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 17.3 | 17.9 | 17.3 |
| standard deviation | ± 1.49 | ± 2.74 | ± 1.70 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 10 | 14 | 5 |
| Male | 22 | 18 | 11 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 3 | 2 | 3 |
| Not Hispanic or Latino | 29 | 30 | 13 |
| Race | | | |
| Units: Subjects | | | |
| White | 29 | 29 | 12 |
| Black or African American | 1 | 1 | 1 |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 1 | 0 | 0 |
| Other | 1 | 2 | 3 |
| Baseline Pain Intensity Score | | | |
| Units: Subjects | | | |
| No Pain (0) | 0 | 0 | 0 |
| Mild Pain (1) | 0 | 0 | 0 |
| Moderate Pain (2) | 11 | 11 | 3 |
| Severe Pain (3) | 21 | 21 | 13 |

| Reporting group values | Placebo | Total | |
|------------------------|---------|-------|--|
| Number of subjects | 17 | 193 | |

| | | | |
|---|----------------|-----|--|
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | 17.7 ± 1.40 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 5 | 77 | |
| Male | 12 | 116 | |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 0 | 10 | |
| Not Hispanic or Latino | 17 | 183 | |
| Race Units: Subjects | | | |
| White | 15 | 177 | |
| Black or African American | 1 | 5 | |
| American Indian or Alaska Native | 0 | 0 | |
| Asian | 0 | 2 | |
| Native Hawaiian or Other Pacific Islander | 0 | 2 | |
| Other | 1 | 7 | |
| Baseline Pain Intensity Score Units: Subjects | | | |
| No Pain (0) | 0 | 0 | |
| Mild Pain (1) | 0 | 0 | |
| Moderate Pain (2) | 5 | 70 | |
| Severe Pain (3) | 12 | 123 | |

End points

End points reporting groups

| | |
|--|---------------------------------|
| Reporting group title | Naproxen Sodium/Caffeine-Dose 1 |
| Reporting group description: Subjects received a single dose of two tablets of naproxen sodium/caffeine (low dose/medium low dose) after extraction of third molars | |
| Reporting group title | Naproxen Sodium/Caffeine-Dose 2 |
| Reporting group description: Subjects received a single dose of two tablets of naproxen sodium/caffeine (low dose/low dose) after extraction of third molars | |
| Reporting group title | Naproxen Sodium/Caffeine-Dose 3 |
| Reporting group description: Subjects received a single dose of one tablet of naproxen sodium/caffeine (low dose/ medium low dose) plus one tablet of placebo after extraction of third molars | |
| Reporting group title | Naproxen Sodium/Caffeine-Dose 4 |
| Reporting group description: Subjects received a single dose of one tablet of naproxen sodium/caffeine (low dose/ low dose) plus one tablet of placebo after extraction of third molars | |
| Reporting group title | Naproxen Sodium |
| Reporting group description: Subjects received a single dose of one tablet of naproxen sodium (low dose) plus one tablet of placebo after extraction of third molars | |
| Reporting group title | Caffeine |
| Reporting group description: Subjects received a single dose of two tablets of caffeine (medium low dose) after extraction of third molars | |
| Reporting group title | Placebo |
| Reporting group description: Subjects received a single dose of two tablets of matching placebo after extraction of third molars | |
| Subject analysis set title | Safety analysis set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All subjects who were randomized and took at least one dose of investigational product. Safety measures were analyzed for all subjects in the safety population | |
| Subject analysis set title | Per protocol set |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Included all subjects in the Safety Population who provided at least one pain assessment after the first dose of the investigational product and did not have any major protocol violations and completed the 12-hour assessments. PP population was used as the primary analysis for the efficacy parameters | |

Primary: Sum of pain intensity difference (SPID) over 8 hours

| | |
|---|---|
| End point title | Sum of pain intensity difference (SPID) over 8 hours ^[1] |
| End point description: Pain intensity is measured using Numerical Rating Scale (from 0 to 10: 0 = no pain, 10 = worst possible pain). For each post dose time point, pain intensity difference (PID) is derived by subtracting the pain intensity at the post dose time point from the baseline intensity score (baseline score – post-baseline score). A positive difference is indicative of improvement. Sum of Pain Intensity Differences (SPIDs) was calculated by multiplying the PID score at each post-dose time point by the duration (in hours) since the preceding time point and then summing these values over the specific time period. SPID over 8 hours ranges from -80 to 80. A higher value indicates a better pain reduction. | |
| End point type | Primary |
| End point timeframe: Up to 8 hours post dose | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistics was provided. Inferential statistics is considered confidential at this point in time.

| End point values | Naproxen Sodium/Caffeine-Dose 1 | Naproxen Sodium/Caffeine-Dose 2 | Naproxen Sodium/Caffeine-Dose 3 | Naproxen Sodium/Caffeine-Dose 4 |
|--------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 32 | 31 | 32 | 32 |
| Units: Scores on a scale*hours | | | | |
| arithmetic mean (standard deviation) | | | | |
| SPID 0-8 | 35.45 (± 14.517) | 37.87 (± 16.876) | 30.70 (± 17.679) | 36.02 (± 14.825) |

| End point values | Naproxen Sodium | Caffeine | Placebo | |
|--------------------------------------|------------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 32 | 16 | 16 | |
| Units: Scores on a scale*hours | | | | |
| arithmetic mean (standard deviation) | | | | |
| SPID 0-8 | 29.95 (± 19.067) | 8.75 (± 21.465) | 6.03 (± 17.810) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Sum of pain intensity differences (SPIDs) from 0 to 2, 4 and 12 hours post-dose

| | |
|-----------------|---|
| End point title | Sum of pain intensity differences (SPIDs) from 0 to 2, 4 and 12 hours post-dose |
|-----------------|---|

End point description:

Pain intensity is measured using Numerical Rating Scale (from 0 to 10: 0 = no pain, 10 = worst possible pain). For each post dose time point, pain intensity difference (PID) is derived by subtracting the pain intensity at the post dose time point from the baseline intensity score (baseline score – post-baseline score). A positive difference is indicative of improvement. Sum of Pain Intensity Differences (SPIDs) was calculated by multiplying the PID score at each post-dose time point by the duration (in hours) since the preceding time point and then summing these values over the specific time period. SPID 0-2 ranges from -20 to 20, SPID 0-4 ranges from -40 to 40 and SPID 0-12 ranges from -120 to 120. A higher value indicates a better pain reduction.

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

End point timeframe:

Up to 2 hours, 4 hours and 12 hours post dose

| End point values | Naproxen Sodium/Caffeine-Dose 1 | Naproxen Sodium/Caffeine-Dose 2 | Naproxen Sodium/Caffeine-Dose 3 | Naproxen Sodium/Caffeine-Dose 4 |
|--------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 32 | 31 | 32 | 32 |
| Units: Scores on a scale*hours | | | | |
| arithmetic mean (standard deviation) | | | | |
| SPID 0-2 | 8.30 (± 3.141) | 8.68 (± 3.789) | 7.17 (± 3.721) | 6.92 (± 3.501) |
| SPID 0-4 | 18.02 (± 6.387) | 19.26 (± 8.019) | 15.58 (± 7.697) | 17.05 (± 7.232) |
| SPID 0-12 | 50.58 (± 24.237) | 52.45 (± 27.305) | 44.80 (± 28.929) | 52.45 (± 23.022) |

| End point values | Naproxen Sodium | Caffeine | Placebo | |
|--------------------------------------|------------------|------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 32 | 16 | 16 | |
| Units: Scores on a scale*hours | | | | |
| arithmetic mean (standard deviation) | | | | |
| SPID 0-2 | 6.05 (± 3.511) | 2.13 (± 4.060) | 1.16 (± 2.925) | |
| SPID 0-4 | 14.33 (± 8.391) | 4.50 (± 9.604) | 2.59 (± 7.625) | |
| SPID 0-12 | 43.08 (± 30.034) | 12.44 (± 32.059) | 1.15 (± 2.833) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Total pain relief (TOTPAR) over 8 hours

| | |
|-----------------|---|
| End point title | Total pain relief (TOTPAR) over 8 hours |
|-----------------|---|

End point description:

Pain relief is measured using Categorical Pain Relief Rating Scale (0 = No relief, 1 = a little relief, 2 = some relief, 3 = a lot of relief, 4 = complete relief). Total Pain Relief is calculated as the area under the curve of pain relief score over time for the given time period by multiplying the pain relief score at each time point by the duration (in hours) since the preceding time point and then summing these values over the specific time period. TOTPAR over 8 hours ranges from 0 to 32, a higher value indicates more pain relief.

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

End point timeframe:

Up to 8 hours post dose

| End point values | Naproxen Sodium/Caffeine-Dose 1 | Naproxen Sodium/Caffeine-Dose 2 | Naproxen Sodium/Caffeine-Dose 3 | Naproxen Sodium/Caffeine-Dose 4 |
|--------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 32 | 31 | 32 | 32 |
| Units: Scores on a scale*hours | | | | |
| arithmetic mean (standard deviation) | | | | |
| TOTPAR 0-8 | 19.58 (± 7.007) | 20.26 (± 7.673) | 17.41 (± 8.063) | 19.53 (± 6.448) |

| End point values | Naproxen Sodium | Caffeine | Placebo | |
|--------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 32 | 16 | 16 | |
| Units: Scores on a scale*hours | | | | |
| arithmetic mean (standard deviation) | | | | |
| TOTPAR 0-8 | 16.27 (± 8.514) | 7.03 (± 9.283) | 5.44 (± 7.709) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Total pain relief (TOTOAR) from 0 to 2, 4 and 12 hours post-dose

| | |
|-----------------|--|
| End point title | Total pain relief (TOTOAR) from 0 to 2, 4 and 12 hours post-dose |
|-----------------|--|

End point description:

Pain relief is measured using Categorical Pain Relief Rating Scale (0 = No relief, 1 = a little relief, 2 = some relief, 3 = a lot of relief, 4 = complete relief). Total Pain Relief is calculated as the area under the curve of pain relief score over time for the given time period by multiplying the pain relief score at each time point by the duration (in hours) since the preceding time point and then summing these values over the specific time period. TOTPAR 0-2 ranges from 0 to 8, TOTPAR 0-4 ranges from 0 to 16, and TOTPAR 0-12 ranges from 0 to 48. A higher value indicates more pain relief

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

End point timeframe:

Up to 2 hours, 4 hours and 12 hours post dose

| End point values | Naproxen Sodium/Caffeine-Dose 1 | Naproxen Sodium/Caffeine-Dose 2 | Naproxen Sodium/Caffeine-Dose 3 | Naproxen Sodium/Caffeine-Dose 4 |
|--------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 32 | 31 | 32 | 32 |
| Units: Scores on a scale*hours | | | | |
| arithmetic mean (standard deviation) | | | | |
| TOTPAR 0-2 | 4.83 (± 1.401) | 4.77 (± 1.731) | 4.22 (± 1.596) | 3.97 (± 1.436) |
| TOTPAR 0-4 | 10.27 (± 2.750) | 10.29 (± 3.449) | 8.84 (± 3.286) | 9.28 (± 2.842) |

| | | | | |
|-------------|-----------------------|-----------------------|-----------------------|-----------------------|
| TOTPAR 0-12 | 28.20 (\pm 12.262) | 28.26 (\pm 12.690) | 25.13 (\pm 13.291) | 28.72 (\pm 10.678) |
|-------------|-----------------------|-----------------------|-----------------------|-----------------------|

| End point values | Naproxen Sodium | Caffeine | Placebo | |
|--------------------------------------|-----------------------|-----------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 32 | 16 | 16 | |
| Units: Scores on a scale*hours | | | | |
| arithmetic mean (standard deviation) | | | | |
| TOTPAR 0-2 | 3.52 (\pm 1.644) | 1.66 (\pm 1.767) | 1.06 (\pm 1.328) | |
| TOTPAR 0-4 | 7.86 (\pm 3.813) | 3.59 (\pm 4.148) | 2.44 (\pm 3.281) | |
| TOTPAR 0-12 | 22.95 (\pm 13.206) | 10.28 (\pm 13.882) | 8.44 (\pm 12.419) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first use of rescue medication

| | |
|--------------------------|--|
| End point title | Time to first use of rescue medication |
| End point description: | |
| 99999: Not Estimable | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 12 hours post dose | |

| End point values | Naproxen Sodium/Caffeine-Dose 1 | Naproxen Sodium/Caffeine-Dose 2 | Naproxen Sodium/Caffeine-Dose 3 | Naproxen Sodium/Caffeine-Dose 4 |
|---------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 32 | 31 | 32 | 32 |
| Units: hours | | | | |
| median (inter-quartile range (Q1-Q3)) | 99999 (99999 to 99999) | 99999 (8.967 to 99999) | 99999 (8.817 to 99999) | 99999 (99999 to 99999) |

| End point values | Naproxen Sodium | Caffeine | Placebo | |
|---------------------------------------|------------------------|------------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 32 | 16 | 16 | |
| Units: hours | | | | |
| median (inter-quartile range (Q1-Q3)) | 99999 (8.125 to 99999) | 2.083 (1.275 to 99999) | 2.125 (1.408 to 99999) | |

Statistical analyses

No statistical analyses for this end point

Secondary: The cumulative percentage of subjects taking rescue medication

| | |
|-----------------|--|
| End point title | The cumulative percentage of subjects taking rescue medication |
|-----------------|--|

End point description:

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

End point timeframe:

Up to 12 hours post dose

| End point values | Naproxen Sodium/Caffeine-Dose 1 | Naproxen Sodium/Caffeine-Dose 2 | Naproxen Sodium/Caffeine-Dose 3 | Naproxen Sodium/Caffeine-Dose 4 |
|-------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 32 | 31 | 32 | 32 |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| 0.5 Hours Post-Dose | 0 | 0 | 0 | 0 |
| 1 Hour Post-Dose | 0 | 0 | 0 | 0 |
| 1.5 Hours Post-Dose | 0 | 3.2 | 3.1 | 0 |
| 2 Hours Post-Dose | 0 | 3.2 | 3.1 | 0 |
| 3 Hours Post-Dose | 0 | 6.5 | 6.3 | 3.1 |
| 4 Hours Post-Dose | 3.1 | 6.5 | 9.4 | 3.1 |
| 5 Hours Post-Dose | 9.4 | 6.5 | 15.6 | 3.1 |
| 6 Hours Post-Dose | 9.4 | 9.7 | 18.8 | 6.3 |
| 7 Hours Post-Dose | 12.5 | 9.7 | 21.9 | 6.3 |
| 8 Hours Post-Dose | 15.6 | 9.7 | 21.9 | 9.4 |
| 9 Hours Post-Dose | 21.9 | 25.8 | 25.0 | 9.4 |
| 10 Hours Post-Dose | 25.0 | 25.8 | 28.1 | 15.6 |
| 11 Hours Post-Dose | 25.0 | 25.8 | 28.1 | 15.6 |
| 12 Hours Post-Dose | 25.0 | 29.0 | 28.1 | 18.8 |

| End point values | Naproxen Sodium | Caffeine | Placebo | |
|-------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 32 | 16 | 16 | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |

| | | | | |
|---------------------|------|------|------|--|
| 0.5 Hours Post-Dose | 0 | 0 | 0 | |
| 1 Hour Post-Dose | 0 | 0 | 0 | |
| 1.5 Hours Post-Dose | 0 | 37.5 | 25.0 | |
| 2 Hours Post-Dose | 0 | 50 | 37.5 | |
| 3 Hours Post-Dose | 15.6 | 56.3 | 56.3 | |
| 4 Hours Post-Dose | 18.8 | 56.3 | 68.8 | |
| 5 Hours Post-Dose | 18.8 | 62.5 | 68.8 | |
| 6 Hours Post-Dose | 21.9 | 68.8 | 68.8 | |
| 7 Hours Post-Dose | 21.9 | 68.8 | 68.8 | |
| 8 Hours Post-Dose | 21.9 | 68.8 | 75.0 | |
| 9 Hours Post-Dose | 28.1 | 68.8 | 75.0 | |
| 10 Hours Post-Dose | 31.3 | 68.8 | 75.0 | |
| 11 Hours Post-Dose | 34.4 | 68.8 | 75.0 | |
| 12 Hours Post-Dose | 34.4 | 75.0 | 75.0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Pain Intensity Difference (PID) at each evaluation

| | |
|---|--|
| End point title | Pain Intensity Difference (PID) at each evaluation |
| End point description: | |
| Pain intensity is measured using Numerical Rating Scale (from 0 to 10: 0 = no pain, 10 = worst possible pain). For each post dose time point, pain intensity difference (PID) is derived by subtracting the pain intensity at the post dose time point from the baseline intensity score (baseline score – post-baseline score). A positive difference is indicative of improvement | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 12 hours post dose | |

| End point values | Naproxen Sodium/Caffeine-Dose 1 | Naproxen Sodium/Caffeine-Dose 2 | Naproxen Sodium/Caffeine-Dose 3 | Naproxen Sodium/Caffeine-Dose 4 |
|--------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 32 | 31 | 32 | 31 |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| 0.5 Hours Post-Dose | 2.3 (± 2.07) | 2.6 (± 1.82) | 2.1 (± 2.23) | 1.4 (± 1.56) |
| 1 Hour Post-Dose | 4.2 (± 1.88) | 4.2 (± 2.44) | 3.7 (± 1.95) | 3.4 (± 2.39) |
| 1.5 Hours Post-Dose | 4.9 (± 1.67) | 5.1 (± 2.26) | 4.3 (± 1.98) | 4.2 (± 2.32) |
| 2 Hours Post-Dose | 5.1 (± 1.76) | 5.5 (± 2.20) | 4.3 (± 2.23) | 4.8 (± 2.23) |
| 3 Hours Post-Dose | 5.0 (± 1.82) | 5.4 (± 2.27) | 4.3 (± 2.33) | 5.0 (± 2.29) |
| 4 Hours Post-Dose | 4.8 (± 2.17) | 5.2 (± 2.59) | 4.1 (± 2.62) | 5.1 (± 2.27) |
| 5 Hours Post-Dose | 4.7 (± 2.28) | 5.0 (± 2.42) | 4.0 (± 2.72) | 5.0 (± 2.25) |
| 6 Hours Post-Dose | 4.6 (± 2.24) | 4.8 (± 2.42) | 3.8 (± 2.87) | 4.9 (± 2.40) |
| 7 Hours Post-Dose | 4.3 (± 2.55) | 4.5 (± 2.45) | 3.8 (± 3.07) | 4.7 (± 2.31) |
| 8 Hours Post-Dose | 4.0 (± 2.53) | 4.2 (± 2.65) | 3.7 (± 3.12) | 4.3 (± 2.29) |
| 9 Hours Post-Dose | 3.8 (± 2.71) | 3.8 (± 3.12) | 3.6 (± 3.00) | 4.2 (± 2.45) |

| | | | | |
|--------------------|--------------|--------------|--------------|--------------|
| 10 Hours Post-Dose | 3.8 (± 2.88) | 3.7 (± 3.04) | 3.4 (± 3.15) | 4.1 (± 2.60) |
| 11 Hours Post-Dose | 3.8 (± 2.92) | 3.5 (± 3.02) | 3.6 (± 3.17) | 4.2 (± 2.79) |
| 12 Hours Post-Dose | 3.8 (± 2.97) | 3.6 (± 3.06) | 3.5 (± 3.38) | 4.0 (± 2.92) |

| End point values | Naproxen Sodium | Caffeine | Placebo | |
|--------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 32 | 16 | 16 | |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| 0.5 Hours Post-Dose | 1.5 (± 1.34) | 0.8 (± 0.98) | 0.5 (± 0.89) | |
| 1 Hour Post-Dose | 2.9 (± 1.88) | 1.2 (± 2.26) | 0.6 (± 1.71) | |
| 1.5 Hours Post-Dose | 3.7 (± 2.16) | 1.2 (± 2.79) | 0.7 (± 1.74) | |
| 2 Hours Post-Dose | 4.1 (± 2.22) | 1.1 (± 2.67) | 0.5 (± 1) | |
| 3 Hours Post-Dose | 4.0 (± 2.83) | 1.1 (± 2.85) | 0.6 (± 2.42) | |
| 4 Hours Post-Dose | 4.3 (± 2.82) | 1.3 (± 3.11) | 0.9 (± 2.78) | |
| 5 Hours Post-Dose | 4.1 (± 2.83) | 1.1 (± 3.14) | 1.0 (± 2.92) | |
| 6 Hours Post-Dose | 3.9 (± 2.88) | 1.1 (± 3.19) | 1.0 (± 3.06) | |
| 7 Hours Post-Dose | 3.9 (± 3.08) | 1.1 (± 3.36) | 0.8 (± 2.49) | |
| 8 Hours Post-Dose | 3.7 (± 2.96) | 0.9 (± 2.95) | 0.7 (± 2.65) | |
| 9 Hours Post-Dose | 3.6 (± 3.14) | 1.1 (± 3.09) | 0.8 (± 2.74) | |
| 10 Hours Post-Dose | 3.3 (± 3.07) | 1.1 (± 3.07) | 0.9 (± 2.99) | |
| 11 Hours Post-Dose | 3.1 (± 3.02) | 0.8 (± 2.99) | 0.9 (± 2.96) | |
| 12 Hours Post-Dose | 3.1 (± 2.97) | 0.8 (± 3.00) | 0.9 (± 2.96) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Peak pain intensity difference (PID)

| | |
|--|--------------------------------------|
| End point title | Peak pain intensity difference (PID) |
| End point description: | |
| Pain intensity is measured using Numerical Rating Scale (from 0 to 10: 0 = no pain, 10 = worst possible pain). Participants circle a number (from 0 to 10) on the Numerical Rating Scale to indicate the severity the pain they are experiencing at baseline and at each post dose time point. For each post dose time point, pain intensity difference (PID) is derived by subtracting the pain intensity at the post dose time point from the baseline intensity score (baseline score - post-baseline score). | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 12 hours post dose | |

| End point values | Naproxen Sodium/Caffeine-Dose 1 | Naproxen Sodium/Caffeine-Dose 2 | Naproxen Sodium/Caffeine-Dose 3 | Naproxen Sodium/Caffeine-Dose 4 |
|--------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 32 | 31 | 32 | 32 |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | 6.0 (± 1.53) | 6.2 (± 1.97) | 5.9 (± 2.01) | 6.3 (± 1.72) |

| End point values | Naproxen Sodium | Caffeine | Placebo | |
|--------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 32 | 16 | 16 | |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | 5.3 (± 2.57) | 2.7 (± 2.94) | 2.3 (± 2.98) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Pain relief score at each evaluation

| | |
|--|--------------------------------------|
| End point title | Pain relief score at each evaluation |
| End point description: | |
| Pain relief is measured using Categorical Pain Relief Rating Scale (0 = No relief, 1 = a little relief, 2 = some relief, 3 = a lot of relief, 4 = complete relief) | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 12 hours post dose | |

| End point values | Naproxen Sodium/Caffeine-Dose 1 | Naproxen Sodium/Caffeine-Dose 2 | Naproxen Sodium/Caffeine-Dose 3 | Naproxen Sodium/Caffeine-Dose 4 |
|--------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 32 | 31 | 32 | 32 |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| 0.5 Hours Post-Dose | 1.6 (± 1.08) | 1.5 (± 0.89) | 1.5 (± 1.02) | 0.9 (± 0.80) |
| 1 Hours Post-Dose | 2.4 (± 0.84) | 2.3 (± 1.22) | 2.2 (± 0.91) | 2.0 (± 1.14) |
| 1.5 Hours Post-Dose | 2.8 (± 0.64) | 2.8 (± 0.99) | 2.3 (± 0.87) | 2.4 (± 0.91) |
| 2 Hours Post-Dose | 2.8 (± 0.85) | 2.9 (± 1.01) | 2.4 (± 1.01) | 2.6 (± 0.79) |
| 3 Hours Post-Dose | 2.8 (± 0.79) | 2.8 (± 0.97) | 2.4 (± 1.04) | 2.6 (± 0.91) |
| 4 Hours Post-Dose | 2.7 (± 1.07) | 2.7 (± 1.19) | 2.3 (± 1.16) | 2.7 (± 0.96) |
| 5 Hours Post-Dose | 2.6 (± 1.16) | 2.6 (± 1.15) | 2.3 (± 1.27) | 2.7 (± 1.00) |
| 6 Hours Post-Dose | 2.4 (± 1.16) | 2.6 (± 1.18) | 2.2 (± 1.35) | 2.7 (± 1.10) |
| 7 Hours Post-Dose | 2.3 (± 1.34) | 2.5 (± 1.15) | 2.1 (± 1.38) | 2.5 (± 1.08) |
| 8 Hours Post-Dose | 2.1 (± 1.33) | 2.3 (± 1.28) | 2.1 (± 1.46) | 2.4 (± 1.19) |
| 9 Hours Post-Dose | 2.2 (± 1.40) | 2.1 (± 1.48) | 2.0 (± 1.45) | 2.3 (± 1.12) |

| | | | | |
|--------------------|--------------|--------------|--------------|--------------|
| 10 Hours Post-Dose | 2.2 (± 1.51) | 2.0 (± 1.43) | 1.8 (± 1.42) | 2.3 (± 1.28) |
| 11 Hours Post-Dose | 2.1 (± 1.52) | 1.9 (± 1.40) | 1.9 (± 1.48) | 2.4 (± 1.34) |
| 12 Hours Post-Dose | 2.2 (± 1.55) | 1.9 (± 1.46) | 2.0 (± 1.51) | 2.2 (± 1.45) |

| End point values | Naproxen Sodium | Caffeine | Placebo | |
|--------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 32 | 16 | 16 | |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| 0.5 Hours Post-Dose | 1.0 (± 0.74) | 0.6 (± 0.62) | 0.4 (± 0.63) | |
| 1 Hours Post-Dose | 1.8 (± 0.91) | 0.9 (± 1.00) | 0.6 (± 0.81) | |
| 1.5 Hours Post-Dose | 2.0 (± 1.05) | 0.9 (± 1.24) | 0.6 (± 0.73) | |
| 2 Hours Post-Dose | 2.2 (± 1.01) | 0.8 (± 1.05) | 0.5 (± 0.82) | |
| 3 Hours Post-Dose | 2.1 (± 1.21) | 0.9 (± 1.24) | 0.6 (± 1.09) | |
| 4 Hours Post-Dose | 2.2 (± 1.26) | 1.0 (± 1.37) | 0.8 (± 1.18) | |
| 5 Hours Post-Dose | 2.2 (± 1.24) | 0.9 (± 1.36) | 0.8 (± 1.18) | |
| 6 Hours Post-Dose | 2.1 (± 1.30) | 0.9 (± 1.45) | 0.8 (± 1.24) | |
| 7 Hours Post-Dose | 2.1 (± 1.29) | 0.9 (± 1.50) | 0.8 (± 1.28) | |
| 8 Hours Post-Dose | 2.0 (± 1.28) | 0.8 (± 1.33) | 0.7 (± 1.25) | |
| 9 Hours Post-Dose | 1.9 (± 1.41) | 0.9 (± 1.36) | 0.8 (± 1.34) | |
| 10 Hours Post-Dose | 1.8 (± 1.41) | 0.9 (± 1.36) | 0.8 (± 1.34) | |
| 11 Hours Post-Dose | 1.4 (± 1.32) | 0.8 (± 1.34) | 0.8 (± 1.34) | |
| 12 Hours Post-Dose | 1.6 (± 1.39) | 0.8 (± 1.34) | 0.8 (± 1.34) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Peak pain relief score

| | |
|--|------------------------|
| End point title | Peak pain relief score |
| End point description: | |
| Pain relief is measured using Categorical Pain Relief Rating Scale (0 = No relief, 1 = a little relief, 2 = some relief, 3 = a lot of relief, 4 = complete relief). At each post-dose time point, participants check the appropriate box (from 0 to 4) on the Categorical Pain Relief Rating Scale to indicate the relief from starting pain at the post dose time points. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 12 hours post dose | |

| End point values | Naproxen Sodium/Caffeine-Dose 1 | Naproxen Sodium/Caffeine-Dose 2 | Naproxen Sodium/Caffeine-Dose 3 | Naproxen Sodium/Caffeine-Dose 4 |
|--------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 32 | 31 | 32 | 32 |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | 3.3 (± 0.62) | 3.2 (± 0.78) | 3.0 (± 0.82) | 3.1 (± 0.66) |

| End point values | Naproxen Sodium | Caffeine | Placebo | |
|--------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 32 | 16 | 16 | |
| Units: Scores on a scale | | | | |
| arithmetic mean (standard deviation) | 2.6 (± 1.01) | 1.6 (± 1.55) | 1.3 (± 1.39) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Global assessment of the investigational product

| | |
|--|--|
| End point title | Global assessment of the investigational product |
| End point description: | |
| Global assessment is performed either at 12 hours post-dose or immediately prior to the first intake of rescue medication. Global assessment is based on the question 'Overall, I would rate the study medication I received: 0=Poor, 1=Fair, 2=Good, 3=Very Good, 4=Excellent.' | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 12 hours post dose | |

| End point values | Naproxen Sodium/Caffeine-Dose 1 | Naproxen Sodium/Caffeine-Dose 2 | Naproxen Sodium/Caffeine-Dose 3 | Naproxen Sodium/Caffeine-Dose 4 |
|-----------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 32 | 31 | 32 | 32 |
| Units: Subjects | | | | |
| Poor (0) | 1 | 1 | 1 | 1 |
| Fair (1) | 2 | 1 | 4 | 2 |
| Good (2) | 5 | 6 | 9 | 7 |
| Very Good (3) | 18 | 14 | 13 | 17 |
| Excellent (4) | 6 | 9 | 5 | 5 |

| End point values | Naproxen Sodium | Caffeine | Placebo | |
|------------------|-----------------|----------|---------|--|
|------------------|-----------------|----------|---------|--|

| Subject group type | Reporting group | Reporting group | Reporting group | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Number of subjects analysed | 32 | 16 | 16 | |
| Units: Subjects | | | | |
| Poor (0) | 4 | 8 | 10 | |
| Fair (1) | 5 | 1 | 2 | |
| Good (2) | 6 | 4 | 1 | |
| Very Good (3) | 14 | 2 | 3 | |
| Excellent (4) | 3 | 1 | 0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: The number of subjects with adverse events

| | |
|-----------------|--|
| End point title | The number of subjects with adverse events |
|-----------------|--|

End point description:

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

End point timeframe:

Up to 5 days post dose

| End point values | Naproxen Sodium/Caffeine-Dose 1 | Naproxen Sodium/Caffeine-Dose 2 | Naproxen Sodium/Caffeine-Dose 3 | Naproxen Sodium/Caffeine-Dose 4 |
|-----------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 32 | 32 | 32 | 32 |
| Units: Subjects | 6 | 3 | 1 | 2 |

| End point values | Naproxen Sodium | Caffeine | Placebo | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 32 | 16 | 17 | |
| Units: Subjects | 3 | 5 | 4 | |

Statistical analyses

No statistical analyses for this end point

Secondary: The number of subjects with clinically significant changes in physical examinations and vital signs

| | |
|-----------------|---|
| End point title | The number of subjects with clinically significant changes in physical examinations and vital signs |
|-----------------|---|

End point description:

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

End point timeframe:

Up to 5 days post dose

| End point values | Naproxen Sodium/Caffeine-Dose 1 | Naproxen Sodium/Caffeine-Dose 2 | Naproxen Sodium/Caffeine-Dose 3 | Naproxen Sodium/Caffeine-Dose 4 |
|-----------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 32 | 32 | 32 | 32 |
| Units: Subjects | 0 | 0 | 0 | 0 |

| End point values | Naproxen Sodium | Caffeine | Placebo | |
|-----------------------------|-----------------|-----------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 32 | 16 | 17 | |
| Units: Subjects | 0 | 0 | 0 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 5 days post-dose

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------------------|
| Reporting group title | Naproxen Sodium/Caffeine-Dose 1 |
|-----------------------|---------------------------------|

Reporting group description:

Subjects received a single dose of two tablets of naproxen sodium/caffeine (low dose/medium low dose) after extraction of third molars

| | |
|-----------------------|---------------------------------|
| Reporting group title | Naproxen Sodium/Caffeine-Dose 3 |
|-----------------------|---------------------------------|

Reporting group description:

Subjects received a single dose of one tablet of naproxen sodium/caffeine (low dose/ medium low dose) plus one tablet of placebo after extraction of third molars

| | |
|-----------------------|---------------------------------|
| Reporting group title | Naproxen Sodium/Caffeine-Dose 2 |
|-----------------------|---------------------------------|

Reporting group description:

Subjects received a single dose of two tablets of naproxen sodium/caffeine (low dose/low dose) after extraction of third molars

| | |
|-----------------------|---------------------------------|
| Reporting group title | Naproxen Sodium/Caffeine-Dose 4 |
|-----------------------|---------------------------------|

Reporting group description:

Subjects received a single dose of one tablet of naproxen sodium/caffeine (low dose/ low dose) plus one tablet of placebo after extraction of third molars

| | |
|-----------------------|-----------------|
| Reporting group title | Naproxen Sodium |
|-----------------------|-----------------|

Reporting group description:

Subjects received a single dose of one tablet of naproxen sodium (low dose) plus one tablet of placebo after extraction of third molars

| | |
|-----------------------|----------|
| Reporting group title | Caffeine |
|-----------------------|----------|

Reporting group description:

Subjects received a single dose of two tablets of caffeine (medium low dose) after extraction of third molars

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects received a single dose of two tablets of matching placebo after extraction of third molars

| Serious adverse events | Naproxen Sodium/Caffeine-Dose 1 | Naproxen Sodium/Caffeine-Dose 3 | Naproxen Sodium/Caffeine-Dose 2 |
|---|---------------------------------|---------------------------------|---------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| Serious adverse events | Naproxen Sodium/Caffeine- | Naproxen Sodium | Caffeine |
|------------------------|---------------------------|-----------------|----------|
|------------------------|---------------------------|-----------------|----------|

| | Dose 4 | | |
|---|----------------|----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 32 (0.00%) | 0 / 16 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| Serious adverse events | Placebo | | |
|---|----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Naproxen Sodium/Caffeine- Dose 1 | Naproxen Sodium/Caffeine- Dose 3 | Naproxen Sodium/Caffeine- Dose 2 |
|---|--|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 6 / 32 (18.75%) | 1 / 32 (3.13%) | 3 / 32 (9.38%) |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 32 (0.00%) | 1 / 32 (3.13%) |
| occurrences (all) | 1 | 0 | 1 |
| Headache | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Syncope | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|--|---------------------|---------------------|---------------------|
| Feeling hot subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 32 (0.00%) 0 | 1 / 32 (3.13%) 1 |
| Pyrexia subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 1 | 0 / 32 (0.00%) 0 | 0 / 32 (0.00%) 0 |
| Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 32 (0.00%) 0 | 0 / 32 (0.00%) 0 |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 1 | 0 / 32 (0.00%) 0 | 1 / 32 (3.13%) 1 |
| Vomiting subjects affected / exposed occurrences (all) | 2 / 32 (6.25%) 2 | 0 / 32 (0.00%) 0 | 0 / 32 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) | 2 / 32 (6.25%) 5 | 1 / 32 (3.13%) 1 | 0 / 32 (0.00%) 0 |
| Paranasal sinus discomfort subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 32 (0.00%) 0 | 0 / 32 (0.00%) 0 |
| Skin and subcutaneous tissue disorders Cold sweat subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 32 (0.00%) 0 | 0 / 32 (0.00%) 0 |
| Hyperhidrosis subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 32 (0.00%) 0 | 1 / 32 (3.13%) 1 |
| Infections and infestations Alveolar osteitis subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 32 (0.00%) 0 | 1 / 32 (3.13%) 1 |
| Cellulitis | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| Non-serious adverse events | Naproxen Sodium/Caffeine- Dose 4 | Naproxen Sodium | Caffeine |
|---|--|-----------------|-----------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | 3 / 32 (9.38%) | 5 / 16 (31.25%) |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 32 (3.13%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 32 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 32 (0.00%) | 2 / 16 (12.50%) |
| occurrences (all) | 0 | 0 | 2 |
| Syncope | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 32 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 32 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Feeling hot | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 32 (3.13%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 32 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 32 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorders | | | |

| | | | |
|--|---------------------|---------------------|----------------------|
| Nausea subjects affected / exposed occurrences (all) | 2 / 32 (6.25%) 2 | 2 / 32 (6.25%) 3 | 4 / 16 (25.00%) 5 |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 32 (0.00%) 0 | 1 / 16 (6.25%) 1 |
| Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 32 (0.00%) 0 | 0 / 16 (0.00%) 0 |
| Paranasal sinus discomfort subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 32 (0.00%) 0 | 0 / 16 (0.00%) 0 |
| Skin and subcutaneous tissue disorders Cold sweat subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 32 (0.00%) 0 | 1 / 16 (6.25%) 1 |
| Hyperhidrosis subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 32 (0.00%) 0 | 0 / 16 (0.00%) 0 |
| Infections and infestations Alveolar osteitis subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 32 (0.00%) 0 | 0 / 16 (0.00%) 0 |
| Cellulitis subjects affected / exposed occurrences (all) | 0 / 32 (0.00%) 0 | 0 / 32 (0.00%) 0 | 0 / 16 (0.00%) 0 |

| | | | |
|--|---------------------|--|--|
| Non-serious adverse events | Placebo | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 4 / 17 (23.53%) | | |
| Cardiac disorders Tachycardia subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | | |
| Nervous system disorders | | | |

| | | | |
|--|----------------------|--|--|
| Dizziness subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | | |
| Headache subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | | |
| Syncope subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | | |
| General disorders and administration site conditions Chest discomfort subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | | |
| Feeling hot subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | | |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | | |
| Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | | |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | | |
| Vomiting subjects affected / exposed occurrences (all) | 2 / 17 (11.76%) 2 | | |
| Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | | |
| Paranasal sinus discomfort | | | |

| | | | |
|--|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| Cold sweat | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infections and infestations | | | |
| Alveolar osteitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | | |
| occurrences (all) | 0 | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 17 (0.00%) | | |
| occurrences (all) | 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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
|---|
| Other pre-specified endpoints (non-key secondary) "Time to first perceptible relief/meaningful relief/perceptible relief confirmed by meaningful relief" and "Cumulative percentage of subjects with at least '2-point PID' over time" were also analyzed |
|---|

Notes: