



Clinical trial results:

A Randomized, Double-Blind, Single-Dose, Parallel, Placebo-Controlled Pivotal Trial to Confirm the Efficacy of a Fixed Dose Combination (FDC) Tablet of Naproxen Sodium and Caffeine to Effectively Alleviate Postsurgical Dental Pain

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2022-003274-22 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 29 January 2024 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 25 July 2024 |
| First version publication date | 25 July 2024 |

Trial information

Trial identification

| | |
|-----------------------|--------------------|
| Sponsor protocol code | BAY2880376 / 22093 |
|-----------------------|--------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT05485805 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Bayer HealthCare LLC, Consumer Health |
| Sponsor organisation address | 100 Bayer Boulevard, Whippany, United States, |
| Public contact | Bayer Clinical Trials Contact, Bayer AG, clinical-trials-contact@bayer.com |
| Scientific contact | Bayer Clinical Trials Contact, 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 | 29 March 2024 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 25 January 2024 |
| Global end of trial reached? | Yes |
| Global end of trial date | 29 January 2024 |
| 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 FDC relative to naproxen sodium 220mg, Caffeine 100 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 | 21 September 2022 |
| 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: 541 |
| Worldwide total number of subjects | 541 |
| 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) | 258 |
| Adults (18-64 years) | 283 |
| From 65 to 84 years | 0 |

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

Subject disposition

Recruitment

Recruitment details:

The clinical study was conducted at a single study site in the United States between 21 September 2022 (first subject first visit) and 29 January 2024 (last subject last visit).

Pre-assignment

Screening details:

A total of 750 participants were screened at a single study center in the United States. 541 participants were randomly assigned to study intervention.

Period 1

| | |
|------------------------------|--------------------------|
| Period 1 title | overall (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/ Caffeine 220/65 mg |
|------------------|-------------------------------------|

Arm description:

Participants received one tablet of the fixed dose combination Naproxen sodium/Caffeine 220/65 mg and one tablet of placebo.

| | |
|--|------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Naproxen sodium/Caffeine 220/65 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

administration as 1 table single dose

| | |
|------------------|--------------------------------------|
| Arm title | Naproxen sodium/Caffeine 2x220/65 mg |
|------------------|--------------------------------------|

Arm description:

Participants received two tablets of the fixed dose combination Naproxen sodium/Caffeine 220/65 mg.

| | |
|--|------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Naproxen sodium/Caffeine 220/65 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

administration as one table single dose

| | |
|------------------|------------------------|
| Arm title | Naproxen sodium 220 mg |
|------------------|------------------------|

Arm description:

Participants received one tablet of Naproxen sodium 220 mg and one tablet of placebo.

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

| | |
|--|------------------------|
| Investigational medicinal product name | Naproxen sodium 220 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: administration as one single tablet Naproxen sodium 220 mg | |
| Arm title | Caffeine 100 mg |
| Arm description: Participants received one tablet Caffeine 100 mg one one tablet of placebo. | |
| Arm type | Experimental |
| Investigational medicinal product name | Caffeine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: Caffeine 100 mg 1 tablet as single dose | |
| Arm title | Placebo |
| Arm description: Participants received two tablets of placebo. | |
| 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: two tablets of placebo as single dose | |

| Number of subjects in period 1 | Naproxen sodium/ Caffeine 220/65 mg | Naproxen sodium/Caffeine 2x220/65 mg | Naproxen sodium 220 mg |
|--------------------------------|--|--|---------------------------|
| | | | |
| Started | 147 | 148 | 147 |
| Completed | 145 | 144 | 142 |
| Not completed | 2 | 4 | 5 |
| Consent withdrawn by subject | 1 | 2 | 2 |
| Adverse event, non-fatal | - | 1 | - |
| Lost to follow-up | 1 | 1 | 3 |

| Number of subjects in period 1 | Caffeine 100 mg | Placebo |
|--------------------------------|-----------------|---------|
| Started | 50 | 49 |
| Completed | 49 | 47 |
| Not completed | 1 | 2 |
| Consent withdrawn by subject | - | 2 |
| Adverse event, non-fatal | - | - |

| | | |
|-------------------|---|---|
| Lost to follow-up | 1 | - |
|-------------------|---|---|

Baseline characteristics

Reporting groups

| | |
|--|--------------------------------------|
| Reporting group title | Naproxen sodium/ Caffeine 220/65 mg |
| Reporting group description: Participants received one tablet of the fixed dose combination Naproxen sodium/Caffeine 220/65 mg and one tablet of placebo. | |
| Reporting group title | Naproxen sodium/Caffeine 2x220/65 mg |
| Reporting group description: Participants received two tablets of the fixed dose combination Naproxen sodium/Caffeine 220/65 mg. | |
| Reporting group title | Naproxen sodium 220 mg |
| Reporting group description: Participants received one tablet of Naproxen sodium 220 mg and one tablet of placebo. | |
| Reporting group title | Caffeine 100 mg |
| Reporting group description: Participants received one tablet Caffeine 100 mg one one tablet of placebo. | |
| Reporting group title | Placebo |
| Reporting group description: Participants received two tablets of placebo. | |

| Reporting group values | Naproxen sodium/ Caffeine 220/65 mg | Naproxen sodium/Caffeine 2x220/65 mg | Naproxen sodium 220 mg |
|---|--|--|---------------------------|
| Number of subjects | 147 | 148 | 147 |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age continuous Units: years | | | |
| arithmetic mean | 18.3 | 18.1 | 18.1 |
| standard deviation | ± 2.13 | ± 1.99 | ± 1.84 |
| Gender categorical Units: Subjects | | | |
| Female | 61 | 70 | 67 |
| Male | 86 | 78 | 80 |

| Reporting group values | Caffeine 100 mg | Placebo | Total |
|------------------------|-----------------|---------|-------|
| Number of subjects | 50 | 49 | 541 |

| | | | |
|---|--------|--------|-----|
| Age categorical Units: Subjects | | | |
| In utero | | | 0 |
| Preterm newborn infants (gestational age < 37 wks) | | | 0 |
| Newborns (0-27 days) | | | 0 |
| Infants and toddlers (28 days-23 months) | | | 0 |
| Children (2-11 years) | | | 0 |
| Adolescents (12-17 years) | | | 0 |
| Adults (18-64 years) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 17.7 | 17.9 | |
| standard deviation | ± 1.82 | ± 2.05 | - |
| Gender categorical Units: Subjects | | | |
| Female | 22 | 23 | 243 |
| Male | 28 | 26 | 298 |

End points

End points reporting groups

| | |
|--|--------------------------------------|
| Reporting group title | Naproxen sodium/ Caffeine 220/65 mg |
| Reporting group description: Participants received one tablet of the fixed dose combination Naproxen sodium/Caffeine 220/65 mg and one tablet of placebo. | |
| Reporting group title | Naproxen sodium/Caffeine 2x220/65 mg |
| Reporting group description: Participants received two tablets of the fixed dose combination Naproxen sodium/Caffeine 220/65 mg. | |
| Reporting group title | Naproxen sodium 220 mg |
| Reporting group description: Participants received one tablet of Naproxen sodium 220 mg and one tablet of placebo. | |
| Reporting group title | Caffeine 100 mg |
| Reporting group description: Participants received one tablet Caffeine 100 mg one one tablet of placebo. | |
| Reporting group title | Placebo |
| Reporting group description: Participants received two tablets of placebo. | |

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

| | |
|---|--|
| End point title | Sum of pain intensity difference (SPID) over 8 hours post-dose |
| End point description: | |
| End point type | Primary |
| End point timeframe: Up to 8 hours post-dose | |

| End point values | Naproxen sodium/ Caffeine 220/65 mg | Naproxen sodium/Caffeine 2x220/65 mg | Naproxen sodium 220 mg | Caffeine 100 mg |
|-------------------------------------|-------------------------------------|--------------------------------------|------------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 147 | 148 | 147 | 50 |
| Units: Points on scale | | | | |
| least squares mean (standard error) | 31.293 (\pm 1.441) | 37.242 (\pm 1.436) | 31.082 (\pm 1.443) | 5.146 (\pm 2.470) |

| End point values | Placebo | | | |
|-------------------------------------|----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 | | | |
| Units: Points on scale | | | | |
| least squares mean (standard error) | 8.622 (\pm 2.521) | | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | group 1 vs group 2 |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Naproxen sodium/Caffeine 2x220/65 mg |
| Number of subjects included in analysis | 295 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.004 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | -5.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.946 |
| upper limit | -1.954 |

| | |
|---|---|
| Statistical analysis title | group 2 vs group 3 |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Naproxen sodium 220 mg |
| Number of subjects included in analysis | 295 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.003 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 6.161 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.161 |
| upper limit | 10.161 |

| | |
|-----------------------------------|--|
| Statistical analysis title | group 3 vs group 4 |
| Comparison groups | Caffeine 100 mg v Naproxen sodium 220 mg |

| | |
|---|--------------------|
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 25.936 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 20.317 |
| upper limit | 31.556 |

| | |
|---|---------------------------|
| Statistical analysis title | group 4 vs group 5 |
| Comparison groups | Caffeine 100 mg v Placebo |
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.325 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | -3.476 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.41 |
| upper limit | 3.457 |

| | |
|---|--|
| Statistical analysis title | group 1 vs group 3 |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Naproxen sodium 220 mg |
| Number of subjects included in analysis | 294 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.918 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 0.211 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.798 |
| upper limit | 4.22 |

| | |
|---|--|
| Statistical analysis title | group 2 vs group 4 |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Caffeine 100 mg |
| Number of subjects included in analysis | 198 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 32.097 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 26.484 |
| upper limit | 37.71 |

| | |
|---|----------------------------------|
| Statistical analysis title | group 3 vs group 5 |
| Comparison groups | Naproxen sodium 220 mg v Placebo |
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 22.46 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 16.753 |
| upper limit | 28.166 |

| | |
|---|---|
| Statistical analysis title | group 1 vs group 4 |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Caffeine 100 mg |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 26.147 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 20.529 |
| upper limit | 31.765 |

| | |
|---|--|
| Statistical analysis title | group 2 vs group 5 |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Placebo |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 28.62 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 22.921 |
| upper limit | 34.32 |

| | |
|---|---|
| Statistical analysis title | group 1 vs group 5 |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Placebo |
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 22.671 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 16.966 |
| upper limit | 28.375 |

Secondary: Sum of pain intensity differences from 0 to 2, 4, 6, 12 and 24 hours post-dose

| | |
|--|--|
| End point title | Sum of pain intensity differences from 0 to 2, 4, 6, 12 and 24 hours post-dose |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| from 0 to 2, 4, 6, 12 and 24 hours post-dose | |

| End point values | Naproxen sodium/ Caffeine 220/65 mg | Naproxen sodium/Caffeine 2x220/65 mg | Naproxen sodium 220 mg | Caffeine 100 mg |
|-------------------------------------|--|--------------------------------------|------------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 147 | 148 | 147 | 50 |
| Units: Points on scale | | | | |
| least squares mean (standard error) | | | | |
| 0-2 hours post-dose | 7.347 (± 0.341) | 8.950 (± 0.340) | 7.973 (± 0.341) | 1.876 (± 0.585) |
| 0-4 hours post-dose | 15.899 (± 0.688) | 19.210 (± 0.686) | 16.627 (± 0.689) | 2.924 (± 1.179) |
| 0-6 hours post-dose | 23.851 (± 1.057) | 28.632 (± 1.053) | 24.381 (± 1.058) | 4.024 (± 1.812) |
| 0-12 hours post-dose | 44.207 (± 2.266) | 51.737 (± 2.258) | 42.907 (± 2.268) | 7.003 (± 3.883) |
| 0-24 hours post-dose | 77.596 (± 4.949) | 83.884 (± 4.930) | 72.796 (± 4.953) | 12.533 (± 8.481) |

| End point values | Placebo | | | |
|-------------------------------------|------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 | | | |
| Units: Points on scale | | | | |
| least squares mean (standard error) | | | | |
| 0-2 hours post-dose | 1.567 (± 0.597) | | | |
| 0-4 hours post-dose | 3.982 (± 1.204) | | | |
| 0-6 hours post-dose | 6.308 (± 1.849) | | | |
| 0-12 hours post-dose | 13.455 (± 3.964) | | | |
| 0-24 hours post-dose | 28.400 (± 8.656) | | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | group 1 vs group 2 |
| Statistical analysis description: | |
| 0-2 hours post-dose | |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Naproxen sodium/Caffeine 2x220/65 mg |
| Number of subjects included in analysis | 295 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | -1.602 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.548 |
| upper limit | -0.656 |

| | |
|---|---|
| Statistical analysis title | group 2 vs group 3 |
| Statistical analysis description: | |
| 0-2 hours post-dose | |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Naproxen sodium 220 mg |
| Number of subjects included in analysis | 295 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.043 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 0.976 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.029 |
| upper limit | 1.923 |

| | |
|---|--|
| Statistical analysis title | group 3 vs group 4 |
| Statistical analysis description: | |
| 0-2 hours post-dose | |
| Comparison groups | Naproxen sodium 220 mg v Caffeine 100 mg |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 6.097 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.766 |
| upper limit | 7.427 |

| | |
|-----------------------------------|--------------------|
| Statistical analysis title | group 4 vs group 5 |
| Statistical analysis description: | |
| 0-2 hours post-dose | |

| | |
|---|---------------------------|
| Comparison groups | Caffeine 100 mg v Placebo |
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.711 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 0.31 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.332 |
| upper limit | 1.951 |

| | |
|---|--|
| Statistical analysis title | group 1 vs group 3 |
| Statistical analysis description: | |
| 0-2 hours post-dose | |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Naproxen sodium 220 mg |
| Number of subjects included in analysis | 294 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.196 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | -0.626 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.575 |
| upper limit | 0.323 |

| | |
|---|--|
| Statistical analysis title | group 2 vs group 4 |
| Statistical analysis description: | |
| 0-2 hours post-dose | |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Caffeine 100 mg |
| Number of subjects included in analysis | 198 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 7.073 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.744 |
| upper limit | 8.402 |

| | |
|---|----------------------------------|
| Statistical analysis title | group 3 vs group 5 |
| Statistical analysis description: | |
| 0-2 hours post-dose | |
| Comparison groups | Naproxen sodium 220 mg v Placebo |
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 6.406 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.055 |
| upper limit | 7.757 |

| | |
|---|---|
| Statistical analysis title | group 1 vs group 4 |
| Statistical analysis description: | |
| 0-2 hours post-dose | |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Caffeine 100 mg |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 5.471 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.141 |
| upper limit | 6.801 |

| | |
|-----------------------------------|--|
| Statistical analysis title | group 2 vs group 5 |
| Statistical analysis description: | |
| 0-2 hours post-dose | |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Placebo |

| | |
|---|--------------------|
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 7.383 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 6.033 |
| upper limit | 8.732 |

| | |
|---|---|
| Statistical analysis title | group 1 vs group 5 |
| Statistical analysis description: | |
| 0-2 hours post-dose | |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Placebo |
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 5.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.43 |
| upper limit | 7.131 |

Secondary: Total pain relief (TOTPAR) from 0 to 2, 4, 6, 8, 12 and 24 hours post-dose

| | |
|--------------------------|--|
| End point title | Total pain relief (TOTPAR) from 0 to 2, 4, 6, 8, 12 and 24 hours post-dose |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| up to 24 hours post-dose | |

| End point values | Naproxen sodium/ Caffeine 220/65 mg | Naproxen sodium/Caffeine 2x220/65 mg | Naproxen sodium 220 mg | Caffeine 100 mg |
|-------------------------------------|--|--------------------------------------|------------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 147 | 148 | 147 | 50 |
| Units: Points on scale | | | | |
| least squares mean (standard error) | | | | |
| 0-2 hours post-dose | 3.284 (± 0.114) | 3.870 (± 0.114) | 3.417 (± 0.115) | 1.047 (± 0.196) |
| 0-4 hours post-dose | 7.781 (± 0.287) | 9.118 (± 0.286) | 8.102 (± 0.287) | 2.120 (± 0.492) |
| 0-6 hours post-dose | 12.098 (± 0.465) | 14.061 (± 0.464) | 12.420 (± 0.466) | 3.228 (± 0.798) |
| 0-8 hours post-dose | 16.227 (± 0.645) | 18.625 (± 0.642) | 16.225 (± 0.645) | 4.327 (± 1.105) |
| 0-12 hours post-dose | 23.512 (± 1.029) | 26.461 (± 1.026) | 22.767 (± 1.030) | 6.264 (± 1.764) |
| 0-24 hours post-dose | 41.596 (± 2.281) | 43.908 (± 2.272) | 39.127 (± 2.283) | 12.047 (± 3.909) |

| End point values | Placebo | | | |
|-------------------------------------|------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 | | | |
| Units: Points on scale | | | | |
| least squares mean (standard error) | | | | |
| 0-2 hours post-dose | 1.216 (± 0.200) | | | |
| 0-4 hours post-dose | 3.168 (± 0.502) | | | |
| 0-6 hours post-dose | 4.870 (± 0.814) | | | |
| 0-8 hours post-dose | 6.552 (± 1.128) | | | |
| 0-12 hours post-dose | 9.700 (± 1.801) | | | |
| 0-24 hours post-dose | 18.975 (± 3.990) | | | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | group 1 vs group 2 |
| Statistical analysis description: | |
| 0-2 hours post-dose | |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Naproxen sodium/Caffeine 2x220/65 mg |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 295 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | -0.586 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.903 |
| upper limit | -0.269 |
| Variability estimate | Standard error of the mean |

| | |
|---|---|
| Statistical analysis title | group 2 vs group 3 |
| Statistical analysis description: | |
| 0-2 hours post-dose | |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Naproxen sodium 220 mg |
| Number of subjects included in analysis | 295 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.005 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 0.454 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.136 |
| upper limit | 0.771 |
| Variability estimate | Standard error of the mean |

| | |
|---|--|
| Statistical analysis title | group 3 vs group 4 |
| Statistical analysis description: | |
| 0-2 hours post-dose | |
| Comparison groups | Naproxen sodium 220 mg v Caffeine 100 mg |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 2.369 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.923 |
| upper limit | 2.815 |
| Variability estimate | Standard error of the mean |

| | |
|---|----------------------------|
| Statistical analysis title | group 4 vs group 5 |
| Statistical analysis description: | |
| 0-2 hours post-dose | |
| Comparison groups | Caffeine 100 mg v Placebo |
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.548 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | -0.169 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.719 |
| upper limit | 0.382 |
| Variability estimate | Standard error of the mean |

| | |
|---|--|
| Statistical analysis title | group 1 vs group 3 |
| Statistical analysis description: | |
| 0-2 hours post-dose | |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Naproxen sodium 220 mg |
| Number of subjects included in analysis | 294 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.415 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | -0.132 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.451 |
| upper limit | 0.186 |
| Variability estimate | Standard error of the mean |

| | |
|---|--|
| Statistical analysis title | group 2 vs group 4 |
| Statistical analysis description: | |
| 0-2 hours post-dose | |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Caffeine 100 mg |
| Number of subjects included in analysis | 198 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 2.823 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.377 |
| upper limit | 3.268 |
| Variability estimate | Standard error of the mean |

| | |
|---|----------------------------------|
| Statistical analysis title | group 3 vs group 5 |
| Statistical analysis description: | |
| 0-2 hours post-dose | |
| Comparison groups | Naproxen sodium 220 mg v Placebo |
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 2.201 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.748 |
| upper limit | 2.654 |
| Variability estimate | Standard error of the mean |

| | |
|-----------------------------------|---|
| Statistical analysis title | group 1 vs group 4 |
| Statistical analysis description: | |
| 0-2 hours post-dose | |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Caffeine 100 mg |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 2.237 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.791 |
| upper limit | 2.683 |
| Variability estimate | Standard error of the mean |

| | |
|---|--|
| Statistical analysis title | group 2 vs group 5 |
| Statistical analysis description: | |
| 0-2 hours post-dose | |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Placebo |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 2.654 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.202 |
| upper limit | 3.106 |
| Variability estimate | Standard error of the mean |

| | |
|---|--|
| Statistical analysis title | group 1 vs group 5 |
| Statistical analysis description: | |
| 0-2 hours post-dose | |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Placebo |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 2.068 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.615 |
| upper limit | 2.521 |
| Variability estimate | Standard error of the mean |

| | |
|---|--|
| Statistical analysis title | group 1 vs group 2 |
| Statistical analysis description: | |
| 0-4 hours post-dose | |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Naproxen sodium/Caffeine 2x220/65 mg |
| Number of subjects included in analysis | 295 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | -1.338 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.133 |
| upper limit | -0.542 |
| Variability estimate | Standard error of the mean |

| | |
|---|---|
| Statistical analysis title | group 2 vs group 3 |
| Statistical analysis description: | |
| 0-4 hours post-dose | |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Naproxen sodium 220 mg |
| Number of subjects included in analysis | 295 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.012 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 1.016 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.22 |
| upper limit | 1.813 |
| Variability estimate | Standard error of the mean |

| | |
|---|--|
| Statistical analysis title | group 3 vs group 4 |
| Statistical analysis description: | |
| 0-4 hours post-dose | |
| Comparison groups | Naproxen sodium 220 mg v Caffeine 100 mg |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 5.982 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.864 |
| upper limit | 7.101 |
| Variability estimate | Standard error of the mean |

| | |
|---|----------------------------|
| Statistical analysis title | group 4 vs group 5 |
| Statistical analysis description: | |
| 0-4 hours post-dose | |
| Comparison groups | Caffeine 100 mg v Placebo |
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.136 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | -1.048 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.428 |
| upper limit | 0.332 |
| Variability estimate | Standard error of the mean |

| | |
|-----------------------------------|--|
| Statistical analysis title | group 1 vs group 3 |
| Statistical analysis description: | |
| 0-4 hours post-dose | |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Naproxen sodium 220 mg |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 294 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.43 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | -0.321 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.119 |
| upper limit | 0.477 |
| Variability estimate | Standard error of the mean |

| | |
|---|--|
| Statistical analysis title | group 2 vs group 4 |
| Statistical analysis description: | |
| 0-4 hours post-dose | |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Caffeine 100 mg |
| Number of subjects included in analysis | 198 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 6.999 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.881 |
| upper limit | 8.116 |
| Variability estimate | Standard error of the mean |

| | |
|---|----------------------------------|
| Statistical analysis title | group 3 vs group 5 |
| Statistical analysis description: | |
| 0-4 hours post-dose | |
| Comparison groups | Naproxen sodium 220 mg v Placebo |
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 4.934 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.798 |
| upper limit | 6.07 |
| Variability estimate | Standard error of the mean |

| | |
|---|---|
| Statistical analysis title | group 1 vs group 4 |
| Statistical analysis description: | |
| 0-4 hours post-dose | |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Caffeine 100 mg |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 5.661 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.543 |
| upper limit | 6.779 |
| Variability estimate | Standard error of the mean |

| | |
|---|--|
| Statistical analysis title | group 2 vs group 5 |
| Statistical analysis description: | |
| 0-4 hours post-dose | |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Placebo |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 5.951 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 4.816 |
| upper limit | 7.085 |
| Variability estimate | Standard error of the mean |

| | |
|-----------------------------------|--------------------|
| Statistical analysis title | group 1 vs group 5 |
|-----------------------------------|--------------------|

| | |
|---|---|
| Statistical analysis description: | |
| 0-4 hours post-dose | |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Placebo |
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 4.613 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.478 |
| upper limit | 5.749 |
| Variability estimate | Standard error of the mean |

| | |
|---|--|
| Statistical analysis title | group 1 vs group 2 |
| Statistical analysis description: | |
| 0-6 hours post-dose | |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Naproxen sodium/Caffeine 2x220/65 mg |
| Number of subjects included in analysis | 295 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.003 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | -1.963 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.254 |
| upper limit | -0.673 |
| Variability estimate | Standard error of the mean |

| | |
|-----------------------------------|---|
| Statistical analysis title | group 2 vs group 3 |
| Statistical analysis description: | |
| 0-6 hours post-dose | |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Naproxen sodium 220 mg |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 295 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.013 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 1.641 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.35 |
| upper limit | 2.933 |
| Variability estimate | Standard error of the mean |

| | |
|---|--|
| Statistical analysis title | group 3 vs group 4 |
| Statistical analysis description: | |
| 0-6 hours post-dose | |
| Comparison groups | Naproxen sodium 220 mg v Caffeine 100 mg |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 9.191 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 7.377 |
| upper limit | 11.006 |
| Variability estimate | Standard error of the mean |

| | |
|---|---------------------------|
| Statistical analysis title | group 4 vs group 5 |
| Statistical analysis description: | |
| 0-6 hours post-dose | |
| Comparison groups | Caffeine 100 mg v Placebo |
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.15 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | -1.642 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.881 |
| upper limit | 0.597 |
| Variability estimate | Standard error of the mean |

| | |
|---|--|
| Statistical analysis title | group 1 vs group 3 |
| Statistical analysis description: | |
| 0-6 hours post-dose | |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Naproxen sodium 220 mg |
| Number of subjects included in analysis | 294 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.625 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | -0.322 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.617 |
| upper limit | 0.972 |
| Variability estimate | Standard error of the mean |

| | |
|---|--|
| Statistical analysis title | group 2 vs group 4 |
| Statistical analysis description: | |
| 0-6 hours post-dose | |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Caffeine 100 mg |
| Number of subjects included in analysis | 198 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 10.833 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 9.02 |
| upper limit | 12.645 |
| Variability estimate | Standard error of the mean |

| | |
|---|----------------------------------|
| Statistical analysis title | group 3 vs group 5 |
| Statistical analysis description: | |
| 0-6 hours post-dose | |
| Comparison groups | Naproxen sodium 220 mg v Placebo |
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 7.55 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.707 |
| upper limit | 9.392 |
| Variability estimate | Standard error of the mean |

| | |
|---|---|
| Statistical analysis title | group 1 vs group 4 |
| Statistical analysis description: | |
| 0-6 hours post-dose | |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Caffeine 100 mg |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 8.869 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 7.055 |
| upper limit | 10.683 |
| Variability estimate | Standard error of the mean |

| | |
|-----------------------------------|--|
| Statistical analysis title | group 2 vs group 5 |
| Statistical analysis description: | |
| 0-6 hours post-dose | |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Placebo |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 9.191 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 7.351 |
| upper limit | 11.031 |
| Variability estimate | Standard error of the mean |

| | |
|---|---|
| Statistical analysis title | group 1 vs group 5 |
| Statistical analysis description: | |
| 0-6 hours post-dose | |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Placebo |
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 7.228 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.386 |
| upper limit | 9.07 |
| Variability estimate | Standard error of the mean |

| | |
|---|--|
| Statistical analysis title | group 1 vs group 2 |
| Statistical analysis description: | |
| 0-8 hours post-dose | |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Naproxen sodium/Caffeine 2x220/65 mg |
| Number of subjects included in analysis | 295 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.009 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | -2.398 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.185 |
| upper limit | -0.61 |
| Variability estimate | Standard error of the mean |

| | |
|---|---|
| Statistical analysis title | group 2 vs group 3 |
| Statistical analysis description: | |
| 0-8 hours post-dose | |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Naproxen sodium 220 mg |
| Number of subjects included in analysis | 295 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.009 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 2.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.61 |
| upper limit | 4.189 |
| Variability estimate | Standard error of the mean |

| | |
|---|--|
| Statistical analysis title | group 3 vs group 4 |
| Statistical analysis description: | |
| 0-8 hours post-dose | |
| Comparison groups | Naproxen sodium 220 mg v Caffeine 100 mg |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 11.898 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 9.384 |
| upper limit | 14.412 |
| Variability estimate | Standard error of the mean |

| | |
|---|----------------------------|
| Statistical analysis title | group 4 vs group 5 |
| Statistical analysis description: | |
| 0-8 hours post-dose | |
| Comparison groups | Caffeine 100 mg v Placebo |
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.159 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | -2.225 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.327 |
| upper limit | 0.877 |
| Variability estimate | Standard error of the mean |

| | |
|---|--|
| Statistical analysis title | group 1 vs group 3 |
| Statistical analysis description: | |
| 0-8 hours post-dose | |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Naproxen sodium 220 mg |
| Number of subjects included in analysis | 294 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.998 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 0.002 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.792 |
| upper limit | 1.795 |
| Variability estimate | Standard error of the mean |

| | |
|-----------------------------------|--|
| Statistical analysis title | group 2 vs group 4 |
| Statistical analysis description: | |
| 0-8 hours post-dose | |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Caffeine 100 mg |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 198 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 14.298 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 11.787 |
| upper limit | 16.809 |
| Variability estimate | Standard error of the mean |

| | |
|---|----------------------------------|
| Statistical analysis title | group 3 vs group 5 |
| Statistical analysis description: | |
| 0-8 hours post-dose | |
| Comparison groups | Naproxen sodium 220 mg v Placebo |
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 9.673 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 7.12 |
| upper limit | 12.226 |
| Variability estimate | Standard error of the mean |

| | |
|---|---|
| Statistical analysis title | group 1 vs group 4 |
| Statistical analysis description: | |
| 0-8 hours post-dose | |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Caffeine 100 mg |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 11.9 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 9.387 |
| upper limit | 14.413 |
| Variability estimate | Standard error of the mean |

| | |
|---|--|
| Statistical analysis title | group 2 vs group 5 |
| Statistical analysis description: | |
| 0-8 hours post-dose | |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Placebo |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 12.073 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 9.523 |
| upper limit | 14.623 |
| Variability estimate | Standard error of the mean |

| | |
|---|---|
| Statistical analysis title | group 1 vs group 5 |
| Statistical analysis description: | |
| 0-8 hours post-dose | |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Placebo |
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 9.675 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 7.123 |
| upper limit | 12.227 |
| Variability estimate | Standard error of the mean |

| | |
|-----------------------------------|--------------------|
| Statistical analysis title | group 1 vs group 2 |
|-----------------------------------|--------------------|

| | |
|---|--|
| Statistical analysis description: | |
| 0-12 hours post-dose | |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Naproxen sodium/Caffeine 2x220/65 mg |
| Number of subjects included in analysis | 295 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.043 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | -2.949 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.803 |
| upper limit | -0.095 |
| Variability estimate | Standard error of the mean |

| | |
|---|---|
| Statistical analysis title | group 2 vs group 3 |
| Statistical analysis description: | |
| 0-12 hours post-dose | |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Naproxen sodium 220 mg |
| Number of subjects included in analysis | 295 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.011 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 3.694 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.837 |
| upper limit | 6.55 |
| Variability estimate | Standard error of the mean |

| | |
|-----------------------------------|--|
| Statistical analysis title | group 3 vs group 4 |
| Statistical analysis description: | |
| 0-12 hours post-dose | |
| Comparison groups | Naproxen sodium 220 mg v Caffeine 100 mg |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 16.504 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 12.49 |
| upper limit | 20.517 |
| Variability estimate | Standard error of the mean |

| | |
|---|----------------------------|
| Statistical analysis title | group 4 vs group 5 |
| Statistical analysis description: | |
| 0-12 hours post-dose | |
| Comparison groups | Caffeine 100 mg v Placebo |
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.173 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | -3.437 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.389 |
| upper limit | 1.515 |
| Variability estimate | Standard error of the mean |

| | |
|---|--|
| Statistical analysis title | group 1 vs group 3 |
| Statistical analysis description: | |
| 0-12 hours post-dose | |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Naproxen sodium 220 mg |
| Number of subjects included in analysis | 294 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.61 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 0.744 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.119 |
| upper limit | 3.608 |
| Variability estimate | Standard error of the mean |

| | |
|---|--|
| Statistical analysis title | group 2 vs group 4 |
| Statistical analysis description: | |
| 0-12 hours post-dose | |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Caffeine 100 mg |
| Number of subjects included in analysis | 198 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 20.197 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 16.189 |
| upper limit | 24.206 |
| Variability estimate | Standard error of the mean |

| | |
|---|----------------------------------|
| Statistical analysis title | group 3 vs group 5 |
| Statistical analysis description: | |
| 0-12 hours post-dose | |
| Comparison groups | Naproxen sodium 220 mg v Placebo |
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 13.067 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 8.992 |
| upper limit | 17.143 |
| Variability estimate | Standard error of the mean |

| | |
|-----------------------------------|--------------------|
| Statistical analysis title | group 2 vs group 4 |
|-----------------------------------|--------------------|

| | |
|---|--|
| Statistical analysis description: | |
| 0-12 hours post-dose | |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Caffeine 100 mg |
| Number of subjects included in analysis | 198 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 17.248 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 13.236 |
| upper limit | 21.261 |
| Variability estimate | Standard error of the mean |

| | |
|---|--|
| Statistical analysis title | group 2 vs group 5 |
| Statistical analysis description: | |
| 0-12 hours post-dose | |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Placebo |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 16.761 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 12.69 |
| upper limit | 20.831 |
| Variability estimate | Standard error of the mean |

| | |
|---|---|
| Statistical analysis title | Copy of group 1 vs group 5 |
| Statistical analysis description: | |
| 0-12 hours post-dose | |
| Comparison groups | Placebo v Naproxen sodium/ Caffeine 220/65 mg |
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 13.812 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 9.738 |
| upper limit | 17.886 |
| Variability estimate | Standard error of the mean |

| | |
|---|--|
| Statistical analysis title | group 1 vs group 2 |
| Statistical analysis description: | |
| 0-24 hours post-dose | |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Naproxen sodium/Caffeine 2x220/65 mg |
| Number of subjects included in analysis | 295 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.473 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | -2.312 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.635 |
| upper limit | 4.011 |
| Variability estimate | Standard error of the mean |

| | |
|---|--|
| Statistical analysis title | group 3 vs group 4 |
| Statistical analysis description: | |
| 0-24 hours post-dose | |
| Comparison groups | Naproxen sodium 220 mg v Caffeine 100 mg |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 27.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 18.188 |
| upper limit | 35.973 |
| Variability estimate | Standard error of the mean |

| | |
|---|----------------------------|
| Statistical analysis title | group 4 vs group 5 |
| Statistical analysis description: | |
| 0-24 hours post-dose | |
| Comparison groups | Caffeine 100 mg v Placebo |
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.215 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | -6.928 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -17.9 |
| upper limit | 4.044 |
| Variability estimate | Standard error of the mean |

| | |
|---|--|
| Statistical analysis title | group 1 vs group 3 |
| Statistical analysis description: | |
| 0-24 hours post-dose | |
| Comparison groups | Naproxen sodium 220 mg v Naproxen sodium/ Caffeine 220/65 mg |
| Number of subjects included in analysis | 294 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.445 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 2.468 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.876 |
| upper limit | 8.813 |
| Variability estimate | Standard error of the mean |

| | |
|-----------------------------------|----------------------------------|
| Statistical analysis title | group 3 vs group 5 |
| Statistical analysis description: | |
| 0-24 hours post-dose | |
| Comparison groups | Naproxen sodium 220 mg v Placebo |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 20.152 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 11.122 |
| upper limit | 29.183 |
| Variability estimate | Standard error of the mean |

| | |
|---|--|
| Statistical analysis title | group 2 vs group 5 |
| Statistical analysis description: | |
| 0-24 hours post-dose | |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Placebo |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 24.933 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 15.914 |
| upper limit | 33.952 |
| Variability estimate | Standard error of the mean |

| | |
|---|---|
| Statistical analysis title | group 1 vs group 5 |
| Statistical analysis description: | |
| 0-24 hours post-dose | |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Placebo |
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Geometric LS means |
| Point estimate | 22.621 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 13.594 |
| upper limit | 31.648 |
| Variability estimate | Standard error of the mean |

Secondary: Time to first use of rescue medication

| | |
|--------------------------|--|
| End point title | Time to first use of rescue medication |
| End point description: | |
| | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 24 hours post-dose | |

| End point values | Naproxen sodium/ Caffeine 220/65 mg | Naproxen sodium/Caffeine 2x220/65 mg | Naproxen sodium 220 mg | Caffeine 100 mg |
|----------------------------------|--|--------------------------------------|------------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 147 ^[1] | 148 ^[2] | 147 ^[3] | 50 |
| Units: Hours | | | | |
| median (confidence interval 95%) | 99999 (17.33 to 99999) | 99999 (14.08 to 99999) | 19.72 (11.08 to 99999) | 2.07 (1.72 to 2.75) |

Notes:

[1] - ""99999" in data entry fields stands for "Not determined" as the value cannot be measured.

[2] - ""99999" in data entry fields stands for "Not determined" as the value cannot be measured.

[3] - ""99999" in data entry fields stands for "Not determined" as the value cannot be measured.

| End point values | Placebo | | | |
|----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 | | | |
| Units: Hours | | | | |
| median (confidence interval 95%) | 2.65 (1.67 to 7.28) | | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | group 1 vs group 2 |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Naproxen sodium/Caffeine 2x220/65 mg |

| | |
|---|---------------|
| Number of subjects included in analysis | 295 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.963 |
| Method | ANCOVA |

| | |
|---|---|
| Statistical analysis title | group 2 vs group 3 |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Naproxen sodium 220 mg |
| Number of subjects included in analysis | 295 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.118 |
| Method | ANCOVA |

| | |
|---|--|
| Statistical analysis title | group 3 vs group 4 |
| Comparison groups | Naproxen sodium 220 mg v Caffeine 100 mg |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |

| | |
|---|---------------------------|
| Statistical analysis title | group 4 vs group 5 |
| Comparison groups | Caffeine 100 mg v Placebo |
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.244 |
| Method | ANCOVA |

| | |
|---|--|
| Statistical analysis title | group 1 vs group 3 |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Naproxen sodium 220 mg |
| Number of subjects included in analysis | 294 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.139 |
| Method | ANCOVA |

| | |
|---|--|
| Statistical analysis title | group 2 vs group 4 |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Naproxen sodium 220 mg |
| Number of subjects included in analysis | 294 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |

| | |
|---|----------------------------------|
| Statistical analysis title | group 3 vs group 5 |
| Comparison groups | Naproxen sodium 220 mg v Placebo |
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |

| | |
|---|---|
| Statistical analysis title | group 1 vs group 4 |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Caffeine 100 mg |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |

| | |
|---|--|
| Statistical analysis title | group 2 vs group 5 |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Placebo |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |

| | |
|-----------------------------------|---|
| Statistical analysis title | group 1 vs group 5 |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Placebo |

| | |
|---|---------------|
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |

Secondary: The cumulative proportion of participants taking rescue medication over the 24 hour period

| | |
|-----------------|--|
| End point title | The cumulative proportion of participants taking rescue medication over the 24 hour period |
|-----------------|--|

End point description:

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

End point timeframe:

Up to 24 hours post-dose

| End point values | Naproxen sodium/ Caffeine 220/65 mg | Naproxen sodium/Caffeine 2x220/65 mg | Naproxen sodium 220 mg | Caffeine 100 mg |
|-----------------------------|---|---|------------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 147 | 148 | 147 | 50 |
| Units: proportion | | | | |
| number (not applicable) | | | | |
| 0.5 hour | 0 | 0 | 0 | 0 |
| less or equal 1 hour | 0.007 | 0 | 0.007 | 0.04 |
| less or equal 1.5 hour | 0.027 | 0.007 | 0.007 | 0.3 |
| less or equal 2 hours | 0.1 | 0.034 | 0.048 | 0.4 |
| less or equal 3 hours | 0.1 | 0.1 | 0.1 | 0.7 |
| less or equal 4 hours | 0.2 | 0.1 | 0.1 | 0.7 |
| less or equal 5 hours | 0.2 | 0.1 | 0.1 | 0.7 |
| less or equal 6 hours | 0.2 | 0.1 | 0.2 | 0.8 |
| less or equal 7 hours | 0.2 | 0.1 | 0.2 | 0.8 |
| less or equal 8 hours | 0.2 | 0.1 | 0.3 | 0.8 |
| less or equal 9 hours | 0.3 | 0.2 | 0.3 | 0.8 |
| less or equal 10 hours | 0.3 | 0.2 | 0.4 | 0.8 |
| less or equal 11 hours | 0.4 | 0.3 | 0.4 | 0.8 |
| less or equal 12 hours | 0.4 | 0.3 | 0.4 | 0.8 |
| less or equal 14 hours | 0.4 | 0.4 | 0.4 | 0.8 |
| less or equal 16 hours | 0.4 | 0.4 | 0.5 | 0.8 |
| less or equal 18 hours | 0.4 | 0.4 | 0.5 | 0.8 |
| less or equal 20 hours | 0.4 | 0.4 | 0.5 | 0.8 |
| less or equal 22 hours | 0.4 | 0.4 | 0.5 | 0.8 |
| less or equal 24 hours | 0.4 | 0.4 | 0.5 | 0.8 |

| End point values | Placebo | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 | | | |
| Units: proportion | | | | |
| number (not applicable) | | | | |
| 0.5 hour | 0 | | | |
| less or equal 1 hour | 0.02 | | | |
| less or equal 1.5 hour | 0.2 | | | |
| less or equal 2 hours | 0.5 | | | |
| less or equal 3 hours | 0.5 | | | |
| less or equal 4hours | 0.6 | | | |
| less or equal 5 hours | 0.6 | | | |
| less or equal 6 hours | 0.6 | | | |
| less or equal 7 hours | 0.6 | | | |
| less or equal 8 hours | 0.6 | | | |
| less or equal 9 hours | 0.7 | | | |
| less or equal 10 hours | 0.7 | | | |
| less or equal 11 hours | 0.7 | | | |
| less or equal 12 hours | 0.7 | | | |
| less or equal 14 hours | 0.7 | | | |
| less or equal 16 hours | 0.7 | | | |
| less or equal 18 hours | 0.7 | | | |
| less or equal 20 hours | 0.7 | | | |
| less or equal 22 hours | 0.7 | | | |
| less or equal 24 hours | 0.7 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first perceptible relief measured by a stopwatch

| | |
|-----------------|--|
| End point title | Time to first perceptible relief measured by a stopwatch |
|-----------------|--|

End point description:

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

End point timeframe:

Up to 24 hours post-dose

| End point values | Naproxen sodium/ Caffeine 220/65 mg | Naproxen sodium/Caffeine 2x220/65 mg | Naproxen sodium 220 mg | Caffeine 100 mg |
|----------------------------------|---|---|------------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 147 | 148 | 147 | 50 |
| Units: Hours | | | | |
| median (confidence interval 95%) | 0.39 (0.33 to 0.42) | 0.35 (0.32 to 0.41) | 0.35 (0.32 to 0.39) | 0.60 (0.42 to 4.13) |

| | | | | |
|----------------------------------|----------------------|--|--|--|
| End point values | Placebo | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 ^[4] | | | |
| Units: Hours | | | | |
| median (confidence interval 95%) | 1.93 (0.51 to 99999) | | | |

Notes:

[4] - "99999" in data entry fields stands for "Not determined" as the value cannot be measured.

Statistical analyses

| | |
|---|--|
| Statistical analysis title | group 1 vs group 2 |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Naproxen sodium/Caffeine 2x220/65 mg |
| Number of subjects included in analysis | 295 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.647 |
| Method | ANCOVA |

| | |
|---|---|
| Statistical analysis title | group 2 vs group 3 |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Naproxen sodium 220 mg |
| Number of subjects included in analysis | 295 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.714 |
| Method | ANCOVA |

| | |
|---|---------------------------|
| Statistical analysis title | group 4 vs group 5 |
| Comparison groups | Caffeine 100 mg v Placebo |
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.065 |
| Method | ANCOVA |

| | |
|-----------------------------------|--|
| Statistical analysis title | group 1 vs group 3 |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Naproxen sodium 220 mg |

| | |
|---|---------------|
| Number of subjects included in analysis | 294 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.742 |
| Method | ANCOVA |

| | |
|---|--|
| Statistical analysis title | group 2 vs group 4 |
| Comparison groups | Caffeine 100 mg v Naproxen sodium/Caffeine 2x220/65 mg |
| Number of subjects included in analysis | 198 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |

| | |
|---|----------------------------------|
| Statistical analysis title | group 3 vs group 5 |
| Comparison groups | Naproxen sodium 220 mg v Placebo |
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |

| | |
|---|---|
| Statistical analysis title | group 1 vs group 4 |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Caffeine 100 mg |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |

| | |
|---|--|
| Statistical analysis title | group 2 vs group 5 |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Placebo |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |

| | |
|---|---|
| Statistical analysis title | group 1 vs group 5 |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Placebo |
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |

Secondary: Time to meaningful relief measured by a stopwatch

| | |
|--------------------------|---|
| End point title | Time to meaningful relief measured by a stopwatch |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 24 hours post-dose | |

| End point values | Naproxen sodium/ Caffeine 220/65 mg | Naproxen sodium/Caffeine 2x220/65 mg | Naproxen sodium 220 mg | Caffeine 100 mg |
|----------------------------------|-------------------------------------|--------------------------------------|------------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 147 | 148 | 147 | 50 ^[5] |
| Units: Hours | | | | |
| median (confidence interval 95%) | 0.83 (0.71 to 0.92) | 0.76 (0.67 to 0.85) | 0.79 (0.67 to 0.93) | 99999 (2.24 to 99999) |

Notes:

[5] - "99999" in data entry fields stands for "Not determined" as the value cannot be measured.

| End point values | Placebo | | | |
|----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 | | | |
| Units: Hours | | | | |
| median (confidence interval 95%) | 5.63 (2.11 to 5.78) | | | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | group 1 vs group 2 |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Naproxen sodium/Caffeine 2x220/65 mg |

| | |
|---|---------------|
| Number of subjects included in analysis | 295 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.162 |
| Method | ANCOVA |

| | |
|---|---|
| Statistical analysis title | group 2 vs group 3 |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Naproxen sodium 220 mg |
| Number of subjects included in analysis | 295 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.319 |
| Method | ANCOVA |

| | |
|---|--|
| Statistical analysis title | group 3 vs group 4 |
| Comparison groups | Naproxen sodium 220 mg v Caffeine 100 mg |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |

| | |
|---|---------------------------|
| Statistical analysis title | group 4 vs group 5 |
| Comparison groups | Caffeine 100 mg v Placebo |
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.343 |
| Method | ANCOVA |

| | |
|---|--|
| Statistical analysis title | group 2 vs group 4 |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Caffeine 100 mg |
| Number of subjects included in analysis | 198 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |

| | |
|---|----------------------------------|
| Statistical analysis title | group 3 vs group 5 |
| Comparison groups | Naproxen sodium 220 mg v Placebo |
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |

| | |
|---|---|
| Statistical analysis title | group 1 vs group 4 |
| Comparison groups | Caffeine 100 mg v Naproxen sodium/ Caffeine 220/65 mg |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |

| | |
|---|--|
| Statistical analysis title | group 2 vs group 5 |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Placebo |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |

| | |
|---|---|
| Statistical analysis title | group 1 vs group 5 |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Placebo |
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |

Secondary: Time to first perceptible relief confirmed by meaningful relief defined as the time to perceptible pain relief

| | |
|-----------------|--|
| End point title | Time to first perceptible relief confirmed by meaningful relief defined as the time to perceptible pain relief |
|-----------------|--|

End point description:

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

End point timeframe:

Up to 24 hours post-dose

| End point values | Naproxen sodium/ Caffeine 220/65 mg | Naproxen sodium/Caffeine 2x220/65 mg | Naproxen sodium 220 mg | Caffeine 100 mg |
|----------------------------------|--|--------------------------------------|------------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 147 | 148 | 147 | 50 ^[6] |
| Units: Hours | | | | |
| median (confidence interval 95%) | 0.83 (0.71 to 0.92) | 0.76 (0.67 to 0.85) | 0.79 (0.67 to 0.93) | 99999 (2.24 to 99999) |

Notes:

[6] - "99999" in data entry fields stands for "Not determined" as the value cannot be measured.

| End point values | Placebo | | | |
|----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 | | | |
| Units: Hours | | | | |
| median (confidence interval 95%) | 5.63 (2.11 to 5.78) | | | |

Statistical analyses

| Statistical analysis title | group 1 vs group 2 |
|---|--|
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Naproxen sodium/Caffeine 2x220/65 mg |
| Number of subjects included in analysis | 295 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.162 |
| Method | ANCOVA |

| Statistical analysis title | group 2 vs group 3 |
|---|---|
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Naproxen sodium 220 mg |
| Number of subjects included in analysis | 295 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.319 |
| Method | ANCOVA |

| Statistical analysis title | group 3 vs group 4 |
|-----------------------------------|--|
| Comparison groups | Naproxen sodium 220 mg v Caffeine 100 mg |

| | |
|---|---------------|
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |

| | |
|---|---------------------------|
| Statistical analysis title | group 4 vs group 45 |
| Comparison groups | Caffeine 100 mg v Placebo |
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.343 |
| Method | ANCOVA |

| | |
|---|----------------------------------|
| Statistical analysis title | Copy of group 1 vs group 3 |
| Comparison groups | Naproxen sodium 220 mg v Placebo |
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.772 |
| Method | ANCOVA |

| | |
|---|--|
| Statistical analysis title | group 2 vs group 4 |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Caffeine 100 mg |
| Number of subjects included in analysis | 198 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |

| | |
|---|----------------------------------|
| Statistical analysis title | group 3 vs group 5 |
| Comparison groups | Naproxen sodium 220 mg v Placebo |
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |

| | |
|---|---|
| Statistical analysis title | group 1 vs group 4 |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Caffeine 100 mg |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |

| | |
|---|--|
| Statistical analysis title | group 2 vs group 5 |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Placebo |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |

| | |
|---|---|
| Statistical analysis title | group 1 vs group 5 |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Placebo |
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | ANCOVA |

| | |
|---|---------------------------------|
| Secondary: Pain intensity difference (PID) | |
| End point title | Pain intensity difference (PID) |
| End point description: | |
| | |
| End point type | Secondary |
| End point timeframe: | |
| up to 24 hours post-dose | |

| End point values | Naproxen sodium/ Caffeine 220/65 mg | Naproxen sodium/Caffeine 2x220/65 mg | Naproxen sodium 220 mg | Caffeine 100 mg |
|--------------------------------------|--|--------------------------------------|------------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 147 | 148 | 147 | 50 |
| Units: Points on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 7.6 (± 1.22) | 7.6 (± 1.20) | 7.8 (± 1.21) | 7.7 (± 1.39) |

| | | | | |
|---------------------|--------------|--------------|--------------|--------------|
| 0.5 hours post-dose | 1.8 (± 1.89) | 2.3 (± 1.91) | 2.4 (± 1.98) | 1.0 (± 1.38) |
| 1 hour post-dose | 3.4 (± 2.40) | 4.3 (± 2.18) | 3.7 (± 2.23) | 0.8 (± 1.67) |
| 1.5 hours post-dose | 4.0 (± 2.40) | 4.9 (± 2.13) | 4.3 (± 2.27) | 0.6 (± 1.68) |
| 2 hours post-dose | 4.4 (± 2.56) | 5.2 (± 2.12) | 4.7 (± 2.30) | 0.7 (± 1.99) |
| 3 hours post-dose | 4.3 (± 2.55) | 5.2 (± 2.28) | 4.4 (± 2.45) | 0.4 (± 1.94) |
| 4 hours post-dose | 4.2 (± 2.54) | 5.1 (± 2.47) | 4.3 (± 2.65) | 0.6 (± 2.19) |
| 5 hours post-dose | 4.0 (± 2.55) | 4.8 (± 2.46) | 4.1 (± 2.73) | 0.5 (± 2.11) |
| 6 hours post-dose | 3.9 (± 2.60) | 4.6 (± 2.48) | 3.8 (± 2.74) | 0.6 (± 2.34) |
| 7 hours post-dose | 3.8 (± 2.61) | 4.4 (± 2.56) | 3.5 (± 2.80) | 0.6 (± 2.30) |
| 8 hours post-dose | 3.6 (± 2.63) | 4.1 (± 2.60) | 3.3 (± 2.88) | 0.6 (± 2.30) |
| 9 hours post dose | 3.5 (± 2.72) | 3.9 (± 2.68) | 3.3 (± 2.96) | 0.6 (± 2.47) |
| 10 hours post-dose | 3.3 (± 2.78) | 3.8 (± 2.81) | 3.1 (± 3.03) | 0.4 (± 2.25) |
| 11 hours post-dose | 3.1 (± 2.84) | 3.6 (± 2.86) | 2.9 (± 3.02) | 0.4 (± 2.34) |
| 12 hours post-dose | 2.9 (± 2.90) | 3.2 (± 2.90) | 2.8 (± 3.07) | 0.4 (± 2.29) |
| 14 hours post-dose | 2.9 (± 2.97) | 2.9 (± 3.01) | 2.6 (± 3.04) | 0.4 (± 2.20) |
| 16 hours post-dose | 2.6 (± 2.99) | 2.7 (± 2.85) | 2.4 (± 3.04) | 0.4 (± 2.27) |
| 18 hours post-dose | 2.7 (± 3.05) | 2.6 (± 2.83) | 2.4 (± 3.02) | 0.4 (± 2.27) |
| 20 hours post-dose | 2.7 (± 3.07) | 2.6 (± 2.81) | 2.5 (± 3.06) | 0.4 (± 2.33) |
| 22 hours post-dose | 2.8 (± 3.19) | 2.7 (± 2.85) | 2.6 (± 3.14) | 0.5 (± 2.55) |
| 24 hours post-dose | 2.9 (± 3.19) | 2.8 (± 2.92) | 2.6 (± 3.20) | 0.6 (± 2.62) |

| End point values | Placebo | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 | | | |
| Units: Points on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 7.7 (± 0.99) | | | |
| 0.5 hours post-dose | 0.6 (± 1.18) | | | |
| 1 hour post-dose | 0.7 (± 1.89) | | | |
| 1.5 hours post-dose | 0.6 (± 2.17) | | | |
| 2 hours post-dose | 0.9 (± 2.48) | | | |
| 3 hours post-dose | 1.1 (± 2.64) | | | |
| 4 hours post-dose | 1.4 (± 2.99) | | | |
| 5 hours post-dose | 1.2 (± 2.84) | | | |
| 6 hours post-dose | 1.2 (± 3.01) | | | |
| 7 hours post-dose | 1.2 (± 2.94) | | | |
| 8 hours post-dose | 1.2 (± 3.00) | | | |
| 9 hours post dose | 1.3 (± 3.15) | | | |
| 10 hours post-dose | 1.3 (± 3.24) | | | |
| 11 hours post-dose | 1.2 (± 3.23) | | | |
| 12 hours post-dose | 1.3 (± 3.32) | | | |
| 14 hours post-dose | 1.3 (± 3.32) | | | |
| 16 hours post-dose | 1.2 (± 3.21) | | | |
| 18 hours post-dose | 1.2 (± 3.22) | | | |
| 20 hours post-dose | 1.2 (± 3.28) | | | |
| 22 hours post-dose | 1.4 (± 3.51) | | | |
| 24 hours post-dose | 1.5 (± 3.63) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Pain relief score

| | |
|---|-------------------|
| End point title | Pain relief score |
| End point description: | |
| Pain Relief Score (PRS): 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 24 hours post-dose | |

| End point values | Naproxen sodium/ Caffeine 220/65 mg | Naproxen sodium/Caffeine 2x220/65 mg | Naproxen sodium 220 mg | Caffeine 100 mg |
|--------------------------------------|---|---|------------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 147 | 148 | 147 | 50 |
| Units: Points on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| 0.5 hours post-dose | 1.3 (± 0.93) | 1.5 (± 1.01) | 1.5 (± 0.97) | 0.7 (± 0.72) |
| 1 hour post-dose | 2.0 (± 1.04) | 2.4 (± 0.9) | 2.1 (± 0.99) | 0.7 (± 0.9) |
| 1.5 hours post-dose | 2.3 (± 1.07) | 2.6 (± 0.87) | 2.3 (± 0.94) | 0.6 (± 0.88) |
| 2 hours post-dose | 2.3 (± 1.13) | 2.7 (± 0.93) | 2.5 (± 0.99) | 0.7 (± 0.95) |
| 3 hours post-dose | 2.3 (± 1.19) | 2.7 (± 1.06) | 2.4 (± 1.11) | 0.5 (± 0.93) |
| 4 hours post-dose | 2.2 (± 1.2) | 2.6 (± 1.18) | 2.3 (± 1.2) | 0.6 (± 0.99) |
| 5 hours post-dose | 2.1 (± 1.24) | 2.5 (± 1.13) | 2.3 (± 1.28) | 0.5 (± 1.03) |
| 6 hours post-dose | 2.2 (± 1.26) | 2.5 (± 1.12) | 2.1 (± 1.28) | 0.6 (± 1.07) |
| 7 hours post-dose | 2.1 (± 1.27) | 2.3 (± 1.16) | 2.0 (± 1.28) | 0.6 (± 1.07) |
| 8 hours post-dose | 2.1 (± 1.28) | 2.2 (± 1.23) | 1.8 (± 1.36) | 0.5 (± 1.03) |
| 9 hours post-dose | 2.0 (± 1.33) | 2.1 (± 1.28) | 1.8 (± 1.39) | 0.5 (± 1.02) |
| 10 hours post-dose | 1.9 (± 1.35) | 2.1 (± 1.35) | 1.7 (± 1.42) | 0.5 (± 1.05) |
| 11 hours post-dose | 1.8 (± 1.38) | 2.0 (± 1.41) | 1.6 (± 1.45) | 0.5 (± 1.07) |
| 12 hours post-dose | 1.7 (± 1.4) | 1.8 (± 1.46) | 1.5 (± 1.47) | 0.5 (± 1.07) |
| 14 hours post-dose | 1.6 (± 1.44) | 1.6 (± 1.51) | 1.4 (± 1.46) | 0.5 (± 1.03) |
| 16 hours post-dose | 1.5 (± 1.45) | 1.5 (± 1.46) | 1.3 (± 1.44) | 0.5 (± 1.03) |
| 18 hours post-dose | 1.5 (± 1.45) | 1.4 (± 1.44) | 1.3 (± 1.43) | 0.5 (± 1.03) |
| 20 hours post-dose | 1.5 (± 1.44) | 1.4 (± 1.44) | 1.3 (± 1.46) | 0.5 (± 1.03) |
| 22 hours post-dose | 1.5 (± 1.51) | 1.5 (± 1.50) | 1.4 (± 1.51) | 0.5 (± 1.18) |
| 24 hours post-dose | 1.6 (± 1.53) | 1.6 (± 1.51) | 1.4 (± 1.56) | 0.5 (± 1.22) |

| End point values | Placebo | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 | | | |
| Units: Points on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| 0.5 hours post-dose | 0 (± 0.65) | | | |
| 1 hour post-dose | 0.8 (± 0.96) | | | |
| 1.5 hours post-dose | 0.8 (± 1.04) | | | |
| 2 hours post-dose | 0.9 (± 1.17) | | | |
| 3 hours post-dose | 1.0 (± 1.25) | | | |
| 4 hours post-dose | 1.0 (± 1.35) | | | |
| 5 hours post-dose | 0.8 (± 1.17) | | | |
| 6 hours post-dose | 0.9 (± 1.3) | | | |
| 7 hours post-dose | 0.9 (± 1.28) | | | |
| 8 hours post-dose | 0.8 (± 1.21) | | | |
| 9 hours post-dose | 0.8 (± 1.28) | | | |
| 10 hours post-dose | 0.8 (± 1.31) | | | |
| 11 hours post-dose | 0.8 (± 1.34) | | | |
| 12 hours post-dose | 0.8 (± 1.34) | | | |
| 14 hours post-dose | 0.8 (± 1.29) | | | |
| 16 hours post-dose | 0.7 (± 1.25) | | | |
| 18 hours post-dose | 0.7 (± 1.25) | | | |
| 20 hours post-dose | 0.8 (± 1.31) | | | |
| 22 hours post-dose | 0.9 (± 1.46) | | | |
| 24 hours post-dose | 0.9 (± 1.51) | | | |

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:

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

End point timeframe:

Up to 24 hours post-dose

| End point values | Naproxen sodium/ Caffeine 220/65 mg | Naproxen sodium/Caffeine 2x220/65 mg | Naproxen sodium 220 mg | Caffeine 100 mg |
|-------------------------------------|--|--------------------------------------|------------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 147 | 148 | 147 | 50 |
| Units: Points on scale | | | | |
| least squares mean (standard error) | 6.12 (\pm 0.11) | 6.26 (\pm 0.11) | 6.22 (\pm 0.11) | 6.30 (\pm 0.18) |

| End point values | Placebo | | | |
|-------------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 | | | |
| Units: Points on scale | | | | |
| least squares mean (standard error) | 6.33 (\pm 0.19) | | | |

Statistical analyses

| Statistical analysis title | group 1 vs group 2 |
|---|--|
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Naproxen sodium/Caffeine 2x220/65 mg |
| Number of subjects included in analysis | 295 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.334 |
| Method | ANCOVA |
| Parameter estimate | geometric LS mean square |
| Point estimate | -0.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.44 |
| upper limit | 0.15 |
| Variability estimate | Standard error of the mean |

| Statistical analysis title | group 2 vs group 3 |
|---|---|
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Naproxen sodium 220 mg |
| Number of subjects included in analysis | 295 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.783 |
| Method | ANCOVA |
| Parameter estimate | geometric LS mean square |
| Point estimate | 0.04 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.25 |
| upper limit | 0.33 |
| Variability estimate | Standard error of the mean |

| | |
|---|--|
| Statistical analysis title | group 3 vs group 4 |
| Comparison groups | Naproxen sodium 220 mg v Caffeine 100 mg |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.687 |
| Method | ANCOVA |
| Parameter estimate | geometric LS mean square |
| Point estimate | -0.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.5 |
| upper limit | 0.33 |
| Variability estimate | Standard error of the mean |

| | |
|---|----------------------------|
| Statistical analysis title | group 4 vs group 5 |
| Comparison groups | Caffeine 100 mg v Placebo |
| Number of subjects included in analysis | 99 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.927 |
| Method | ANCOVA |
| Parameter estimate | geometric LS mean square |
| Point estimate | -0.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.53 |
| upper limit | 0.49 |
| Variability estimate | Standard error of the mean |

| | |
|-----------------------------------|--|
| Statistical analysis title | group 1 vs group 3 |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Naproxen sodium 220 mg |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 294 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.492 |
| Method | ANCOVA |
| Parameter estimate | geometric LS mean square |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 0.19 |
| Variability estimate | Standard error of the mean |

| | |
|---|--|
| Statistical analysis title | group 2 vs group 4 |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Caffeine 100 mg |
| Number of subjects included in analysis | 198 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.836 |
| Method | ANCOVA |
| Parameter estimate | geometric LS mean square |
| Point estimate | -0.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.46 |
| upper limit | 0.37 |
| Variability estimate | Standard error of the mean |

| | |
|---|---|
| Statistical analysis title | group 3 vs group 5 |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Placebo |
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.611 |
| Method | ANCOVA |
| Parameter estimate | geometric LS mean square |
| Point estimate | -0.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.53 |
| upper limit | 0.31 |
| Variability estimate | Standard error of the mean |

| | |
|---|---|
| Statistical analysis title | group 1 vs group 4 |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Caffeine 100 mg |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.371 |
| Method | ANCOVA |
| Parameter estimate | geometric LS mean square |
| Point estimate | -0.19 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.6 |
| upper limit | 0.22 |
| Variability estimate | Standard error of the mean |

| | |
|---|--|
| Statistical analysis title | group 2 vs group 5 |
| Comparison groups | Naproxen sodium/Caffeine 2x220/65 mg v Placebo |
| Number of subjects included in analysis | 197 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.752 |
| Method | ANCOVA |
| Parameter estimate | geometric LS mean square |
| Point estimate | -0.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.49 |
| upper limit | 0.35 |
| Variability estimate | Standard error of the mean |

| | |
|---|---|
| Statistical analysis title | group 1 vs group 5 |
| Comparison groups | Naproxen sodium/ Caffeine 220/65 mg v Placebo |
| Number of subjects included in analysis | 196 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.321 |
| Method | ANCOVA |
| Parameter estimate | geometric LS mean square |
| Point estimate | -0.21 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.63 |
| upper limit | 0.21 |
| Variability estimate | Standard error of the mean |

Secondary: Number of participants with certain peak pain relief score

| | |
|--|--|
| End point title | Number of participants with certain peak pain relief score |
| End point description: | |
| Number of participants with pain relief score 4, 3, 2, 1 | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 24 hours post-dose | |

| End point values | Naproxen sodium/ Caffeine 220/65 mg | Naproxen sodium/Caffeine 2x220/65 mg | Naproxen sodium 220 mg | Caffeine 100 mg |
|-----------------------------|--|--------------------------------------|------------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 147 | 148 | 147 | 50 |
| Units: participants | | | | |
| Pain relief score 4 | 31 | 47 | 36 | 15 |
| Pain relief score 3 | 101 | 85 | 102 | 31 |
| Pain relief score 2 | 14 | 15 | 9 | 4 |
| Pain relief score 1 | 1 | 1 | 0 | 0 |

| End point values | Placebo | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 | | | |
| Units: participants | | | | |
| Pain relief score 4 | 15 | | | |
| Pain relief score 3 | 29 | | | |
| Pain relief score 2 | 5 | | | |
| Pain relief score 1 | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative percent of participants with 'at least a 2-point PID' over time

| | |
|-----------------|--|
| End point title | Cumulative percent of participants with 'at least a 2-point PID' |
|-----------------|--|

over time

End point description:

End point type Secondary

End point timeframe:

Up to 24 hours post-dose

| End point values | Naproxen sodium/ Caffeine 220/65 mg | Naproxen sodium/Caffeine 2x220/65 mg | Naproxen sodium 220 mg | Caffeine 100 mg |
|-----------------------------|---|---|------------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 147 | 148 | 147 | 50 |
| Units: percentage | | | | |
| number (not applicable) | | | | |
| 0.5 hour post-dose | 50.3 | 62.8 | 60.5 | 32.0 |
| less or equal 1 hour | 78.2 | 86.5 | 86.4 | 40.0 |
| less or equal 1.5 hour | 87.1 | 94.6 | 92.5 | 46.0 |
| less or equal 2 hours | 92.5 | 98.0 | 94.6 | 64.0 |
| less or equal 3 hours | 98.0 | 99.3 | 98.0 | 86.0 |
| less or equal 4 hours | 98.6 | 99.3 | 99.3 | 94.0 |
| less or equal 5 hours | 98.6 | 99.3 | 99.3 | 98.0 |
| less or equal 6 hours | 99.3 | 99.3 | 99.3 | 100 |
| less or equal 7 hours | 99.3 | 99.3 | 99.3 | 100 |
| less or equal 8 hours | 99.3 | 99.3 | 100 | 100 |
| less or equal 9 hours | 99.3 | 99.3 | 100 | 100 |
| less or equal 10 hours | 99.3 | 99.3 | 100 | 100 |
| less or equal 11 hours | 99.3 | 99.3 | 100 | 100 |
| less or equal 12 hours | 100 | 99.3 | 100 | 100 |
| less or equal 14 hours | 100 | 99.3 | 100 | 100 |
| less or equal 16 hours | 100 | 99.3 | 100 | 100 |
| less or equal 18 hours | 100 | 99.3 | 100 | 100 |
| less or equal 20 hours | 100 | 99.3 | 100 | 100 |
| less or equal 22 hours | 100 | 99.3 | 100 | 100 |
| less or equal 24 hours | 100 | 99.3 | 100 | 100 |

| End point values | Placebo | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 | | | |
| Units: percentage | | | | |
| number (not applicable) | | | | |
| 0.5 hour post-dose | 18.4 | | | |
| less or equal 1 hour | 26.5 | | | |
| less or equal 1.5 hour | 40.8 | | | |
| less or equal 2 hours | 71.4 | | | |
| less or equal 3 hours | 87.8 | | | |
| less or equal 4 hours | 95.9 | | | |

| | | | | |
|------------------------|------|--|--|--|
| less or equal 5 hours | 98.0 | | | |
| less or equal 6 hours | 98.0 | | | |
| less or equal 7 hours | 98.0 | | | |
| less or equal 8 hours | 98.0 | | | |
| less or equal 9 hours | 98.0 | | | |
| less or equal 10 hours | 98.0 | | | |
| less or equal 11 hours | 98.0 | | | |
| less or equal 12 hours | 98.0 | | | |
| less or equal 14 hours | 98.0 | | | |
| less or equal 16 hours | 98.0 | | | |
| less or equal 18 hours | 98.0 | | | |
| less or equal 20 hours | 98.0 | | | |
| less or equal 22 hours | 98.0 | | | |
| less or equal 24 hours | 98.0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Global assessment of pain relief of the investigational product

| | |
|-----------------|---|
| End point title | Global assessment of pain relief of the investigational product |
|-----------------|---|

End point description:

Number of participants with overall rating poor, fair, good, very good, excellent 24 hour post-dose

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

End point timeframe:

24 hours post-dose

| End point values | Naproxen sodium/ Caffeine 220/65 mg | Naproxen sodium/Caffeine 2x220/65 mg | Naproxen sodium 220 mg | Caffeine 100 mg |
|-----------------------------|---|---|------------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 147 | 148 | 147 | 50 |
| Units: participants | | | | |
| poor | 16 | 5 | 11 | 26 |
| fair | 10 | 12 | 12 | 10 |
| good | 35 | 23 | 38 | 8 |
| very good | 56 | 69 | 58 | 5 |
| excellent | 30 | 37 | 28 | 1 |

| End point values | Placebo | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 | | | |
| Units: participants | | | | |

| | | | | |
|-----------|----|--|--|--|
| poor | 27 | | | |
| fair | 5 | | | |
| good | 3 | | | |
| very good | 9 | | | |
| excellent | 3 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with adverse events

| | |
|------------------------|--|
| End point title | Number of participants 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 220/65 mg | Naproxen sodium/Caffeine 2x220/65 mg | Naproxen sodium 220 mg | Caffeine 100 mg |
|-----------------------------|---|---|------------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 147 | 148 | 147 | 50 |
| Units: participants | 28 | 18 | 27 | 7 |

| End point values | Placebo | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 | | | |
| Units: participants | 7 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with significant changes in vital signs since baseline

| | |
|------------------------|---|
| End point title | Number of participants with significant changes in vital signs since baseline |
| End point description: | |
| End point type | Secondary |

End point timeframe:
Up to 5 days post-dose

| End point values | Naproxen sodium/ Caffeine 220/65 mg | Naproxen sodium/Caffeine 2x220/65 mg | Naproxen sodium 220 mg | Caffeine 100 mg |
|-----------------------------|---|---|------------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 147 | 148 | 147 | 50 |
| Units: participants | | | | |
| Bradycardia | 1 | 1 | 0 | 0 |
| Tachycardia | 1 | 0 | 3 | 0 |
| Hypertension | 2 | 0 | 0 | 0 |
| Hypotension | 1 | 3 | 4 | 0 |

| End point values | Placebo | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 | | | |
| Units: participants | | | | |
| Bradycardia | 0 | | | |
| Tachycardia | 0 | | | |
| Hypertension | 0 | | | |
| Hypotension | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were considered treatment-emergent if they had started or worsened after the first dose of the investigational medicinal product (IMP) until 2-5 after end of treatment

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 25.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------------|
| Reporting group title | Fixed Dose Combination |
|-----------------------|------------------------|

Reporting group description:

Fixed Dose Combination of Naproxen Sodium 220 mg and Caffeine 65 mg

| | |
|-----------------------|------------------------|
| Reporting group title | Fixed Dose Combination |
|-----------------------|------------------------|

Reporting group description:

Fixed Dose Combination of twice Naproxen Sodium 220 mg and Caffeine 65 mg

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

Reporting group description:

Placebo

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

Reporting group description:

Caffeine 100 mg

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

Reporting group description:

Naproxen sodium 220 mg

| Serious adverse events | Fixed Dose Combination | Fixed Dose Combination | Placebo |
|---|------------------------|------------------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 0 / 148 (0.00%) | 0 / 49 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| Serious adverse events | Caffeine | Naproxen Sodium | |
|---|----------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 147 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |

| Non-serious adverse events | Fixed Dose Combination | Fixed Dose Combination | Placebo |
|---|--|--|---|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 19 / 147 (12.93%) | 11 / 148 (7.43%) | 4 / 49 (8.16%) |
| Injury, poisoning and procedural complications Wound haemorrhage subjects affected / exposed occurrences (all) | 0 / 147 (0.00%) 0 | 1 / 148 (0.68%) 1 | 0 / 49 (0.00%) 0 |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) Hypotension subjects affected / exposed occurrences (all) Thrombosis subjects affected / exposed occurrences (all) | 2 / 147 (1.36%) 2 1 / 147 (0.68%) 1 0 / 147 (0.00%) 0 | 0 / 148 (0.00%) 0 1 / 148 (0.68%) 1 0 / 148 (0.00%) 0 | 0 / 49 (0.00%) 0 0 / 49 (0.00%) 0 0 / 49 (0.00%) 0 |
| Cardiac disorders Bradycardia subjects affected / exposed occurrences (all) Tachycardia subjects affected / exposed occurrences (all) | 1 / 147 (0.68%) 1 1 / 147 (0.68%) 1 | 0 / 148 (0.00%) 0 0 / 148 (0.00%) 0 | 0 / 49 (0.00%) 0 0 / 49 (0.00%) 0 |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Syncope subjects affected / exposed occurrences (all) | 3 / 147 (2.04%) 4 4 / 147 (2.72%) 4 0 / 147 (0.00%) 0 | 2 / 148 (1.35%) 2 0 / 148 (0.00%) 0 2 / 148 (1.35%) 2 | 1 / 49 (2.04%) 1 3 / 49 (6.12%) 3 0 / 49 (0.00%) 0 |
| General disorders and administration site conditions | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| Chills | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 0 / 148 (0.00%) | 0 / 49 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pain | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 148 (0.00%) | 0 / 49 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 148 (0.00%) | 0 / 49 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ear and labyrinth disorders | | | |
| Deafness | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 148 (0.68%) | 0 / 49 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 148 (0.68%) | 0 / 49 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 148 (0.00%) | 0 / 49 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 0 / 148 (0.00%) | 0 / 49 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 1 / 148 (0.68%) | 0 / 49 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 6 / 148 (4.05%) | 0 / 49 (0.00%) |
| occurrences (all) | 1 | 7 | 0 |
| Toothache | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 148 (0.00%) | 0 / 49 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 0 / 148 (0.00%) | 0 / 49 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|--|----------------------|----------------------|---------------------|
| Dyspnoea subjects affected / exposed occurrences (all) | 0 / 147 (0.00%) 0 | 0 / 148 (0.00%) 0 | 0 / 49 (0.00%) 0 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 0 / 147 (0.00%) 0 | 0 / 148 (0.00%) 0 | 0 / 49 (0.00%) 0 |
| Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all) | 0 / 147 (0.00%) 0 | 1 / 148 (0.68%) 1 | 0 / 49 (0.00%) 0 |
| Rash subjects affected / exposed occurrences (all) | 1 / 147 (0.68%) 1 | 0 / 148 (0.00%) 0 | 0 / 49 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all) | 0 / 147 (0.00%) 0 | 0 / 148 (0.00%) 0 | 0 / 49 (0.00%) 0 |
| Infections and infestations Alveolar osteitis subjects affected / exposed occurrences (all) | 4 / 147 (2.72%) 4 | 0 / 148 (0.00%) 0 | 0 / 49 (0.00%) 0 |
| Candida infection subjects affected / exposed occurrences (all) | 0 / 147 (0.00%) 0 | 0 / 148 (0.00%) 0 | 1 / 49 (2.04%) 1 |
| Post procedural infection subjects affected / exposed occurrences (all) | 0 / 147 (0.00%) 0 | 0 / 148 (0.00%) 0 | 0 / 49 (0.00%) 0 |

| Non-serious adverse events | Caffeine | Naproxen Sodium | |
|---|---------------------|----------------------|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 3 / 50 (6.00%) | 23 / 147 (15.65%) | |
| Injury, poisoning and procedural complications Wound haemorrhage subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 147 (0.00%) 0 | |
| Vascular disorders | | | |

| | | | |
|---|---------------------|----------------------|--|
| Hypertension subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 147 (0.00%) 0 | |
| Hypotension subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 3 / 147 (2.04%) 3 | |
| Thrombosis subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 2 / 147 (1.36%) 2 | |
| Cardiac disorders Bradycardia subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 147 (0.00%) 0 | |
| Tachycardia subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 3 / 147 (2.04%) 3 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 7 / 147 (4.76%) 7 | |
| Headache subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 2 | 1 / 147 (0.68%) 1 | |
| Syncope subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 147 (0.00%) 0 | |
| General disorders and administration site conditions Chills subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 1 / 147 (0.68%) 1 | |
| Pain subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 147 (0.00%) 0 | |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 147 (0.00%) 0 | |

| | | | |
|---|----------------|-----------------|--|
| Ear and labyrinth disorders | | | |
| Deafness | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 147 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 147 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 147 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 147 (0.68%) | |
| occurrences (all) | 0 | 1 | |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 147 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 5 / 147 (3.40%) | |
| occurrences (all) | 0 | 5 | |
| Toothache | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 147 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 9 / 147 (6.12%) | |
| occurrences (all) | 0 | 12 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 147 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 2 / 147 (1.36%) | |
| occurrences (all) | 0 | 2 | |
| Skin and subcutaneous tissue disorders | | | |
| Hyperhidrosis | | | |

| | | | |
|--|---------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 147 (0.00%) 0 | |
| Rash subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 147 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 1 / 147 (0.68%) 1 | |
| Infections and infestations Alveolar osteitis subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 1 / 147 (0.68%) 1 | |
| Candida infection subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 147 (0.00%) 0 | |
| Post procedural infection subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 1 / 147 (0.68%) 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 28 April 2022 | The randomization schedule was changed from 2:2:2:1:1 to 3:3:3:1:1 |
| 07 November 2022 | <ul style="list-style-type: none">Specified that at the timepoints of 16, 18, and 20 hours for Pain Intensity Difference (PID), Pain Relief scores, Pain Intensity NRS, and Categorical Pain Relief, the assessments would be performed only if the participant was awake;Added a secondary endpoint of 'time and cumulative proportion of achieving complete pain relief'. This endpoint was to be analyzed similarly as for the time to first use of rescue medication. Cumulative percent of participants with 'at least a 2 point PID' and cumulative percent of participants achieving complete pain relief were to be plotted over time and were to be analyzed using Chi-square tests;Changed the exclusion criterion of Nicotine containing products from 'midnight prior to surgery until discharge' to 'from 24 hours prior to surgery until discharge';Added a timepoint for vital sign measurement at 12 hours post-dose. Further clarifications and adjustments |
| 13 March 2023 | <ul style="list-style-type: none">Added a window period for vital signs measurements;Added a window period for participants who did not meet the randomization criteria within 4.5 hours from last suture or 14:30 hours. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported