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

Summary

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

Results information

Result version number	v1
This version publication date	13 September 2020
First version publication date	13 September 2020

Trial information

Trial identification

Sponsor protocol code	BAY2880376/21069

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 March 2020
Is this the analysis of the primary completion data?	No

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

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 November 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 193
Worldwide total number of subjects	193
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	91
Adults (18-64 years)	102
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at a single center in United States between 12-Nov-2019 (first subject first visit) and 02-Mar-2020 (last subject last visit)

Pre-assignment

Screening details:

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

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Naproxen Sodium/Caffeine 440/200 mg

Arm description:

Subjects received 440 mg naproxen sodium and 200 mg caffeine after extraction of third molars

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

Dosage and administration details:

Single dose of 2 tablets of 220/100 mg Naproxen sodium/Caffeine

Arm title	Naproxen Sodium/Caffeine 440/130 mg

Arm description:

Subjects received 440 mg naproxen sodium and 130 mg caffeine after extraction of third molars

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

Dosage and administration details:

Single dose of 2 tablets of 220/65 mg Naproxen sodium/Caffeine

Arm title	Naproxen Sodium/Caffeine 220/100 mg

Arm description:

Subjects received 220 mg naproxen sodium and 100 mg caffeine after extraction of third molars

Arm type	Experimental

Investigational medicinal product name	Naproxen sodium/Caffeine
Investigational medicinal product code	BAY2880376
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Single dose of 1 tablet of 220/100 mg Naproxen sodium/Caffeine

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

Dosage and administration details:

Single dose of 1 tablet of matching Placebo

Arm title	Naproxen Sodium/Caffeine 220/65 mg

Arm description:

Subjects received 220 mg naproxen sodium and 65 mg caffeine after extraction of third molars

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

Dosage and administration details:

Single dose of 1 tablet of 220/65 mg Naproxen sodium/Caffeine

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

Dosage and administration details:

Single dose of 1 tablet of matching Placebo

Arm title	Naproxen Sodium 220 mg

Arm description:

Subjects received 220 mg naproxen sodium after extraction of third molars

Arm type	Active comparator
Investigational medicinal product name	Naproxen sodium
Investigational medicinal product code	BAY117031
Other name	Aleve
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Single dose of 1 tablet of 220 mg Naproxen sodium

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

Dosage and administration details:

Single dose of 1 tablet of matching Placebo

Arm title	Caffeine 200 mg

Arm description:	
Subjects received 200 mg caffeine after extraction of third molars	
Arm type	Active comparator
Investigational medicinal product name	Caffeine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Single dose of 2 tablets of 100 mg Caffeine	
Arm title	Placebo
Arm description:	
Subjects received placebo after extraction of third molars	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Single dose of 2 tablets of matching Placebo	

Number of subjects in period 1	Naproxen Sodium/Caffeine 440/200 mg	Naproxen Sodium/Caffeine 440/130 mg	Naproxen Sodium/Caffeine 220/100 mg
Started	32	32	32
Completed	32	31	32
Not completed	0	1	0
Investigator Decision	-	1	-

Number of subjects in period 1	Naproxen Sodium/Caffeine 220/65 mg	Naproxen Sodium 220 mg	Caffeine 200 mg
Started	32	32	16
Completed	32	32	16
Not completed	0	0	0
Investigator Decision	-	-	-

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

Baseline characteristics

Reporting groups	
Reporting group title	Naproxen Sodium/Caffeine 440/200 mg
Reporting group description:	
Subjects received 440 mg naproxen sodium and 200 mg caffeine after extraction of third molars	
Reporting group title	Naproxen Sodium/Caffeine 440/130 mg
Reporting group description:	
Subjects received 440 mg naproxen sodium and 130 mg caffeine after extraction of third molars	
Reporting group title	Naproxen Sodium/Caffeine 220/100 mg
Reporting group description:	
Subjects received 220 mg naproxen sodium and 100 mg caffeine after extraction of third molars	
Reporting group title	Naproxen Sodium/Caffeine 220/65 mg
Reporting group description:	
Subjects received 220 mg naproxen sodium and 65 mg caffeine after extraction of third molars	
Reporting group title	Naproxen Sodium 220 mg
Reporting group description:	
Subjects received 220 mg naproxen sodium after extraction of third molars	
Reporting group title	Caffeine 200 mg
Reporting group description:	
Subjects received 200 mg caffeine after extraction of third molars	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo after extraction of third molars	

Reporting group values	Naproxen Sodium/Caffeine 440/200 mg	Naproxen Sodium/Caffeine 440/130 mg	Naproxen Sodium/Caffeine 220/100 mg
Number of subjects	32	32	32
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	17.0	17.4	17.1
standard deviation	± 1.03	± 2.42	± 1.34
Gender categorical Units: Subjects			
Female	13	14	16
Male	19	18	16
Ethnicity Units: Subjects			
Hispanic or Latino	2	0	0
Not Hispanic or Latino	30	32	32
Race Units: Subjects			
White	31	31	30
Black or African American	0	0	1
American Indian or Alaska Native	0	0	0
Asian	0	1	1

Native Hawaiian or Other Pacific Islander	1	0	0
Other	0	0	0
Baseline Pain Intensity Score Units: Subjects			
No Pain (0)	0	0	0
Mild Pain (1)	0	0	0
Moderate Pain (2)	15	13	12
Severe Pain (3)	17	19	20

Reporting group values	Naproxen Sodium/Caffeine 220/65 mg	Naproxen Sodium 220 mg	Caffeine 200 mg
Number of subjects	32	32	16
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	17.3	17.9	17.3
standard deviation	± 1.49	± 2.74	± 1.70
Gender categorical Units: Subjects			
Female	10	14	5
Male	22	18	11
Ethnicity Units: Subjects			
Hispanic or Latino	3	2	3
Not Hispanic or Latino	29	30	13
Race Units: Subjects			
White	29	29	12
Black or African American	1	1	1
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	1	0	0
Other	1	2	3
Baseline Pain Intensity Score Units: Subjects			
No Pain (0)	0	0	0
Mild Pain (1)	0	0	0
Moderate Pain (2)	11	11	3
Severe Pain (3)	21	21	13

Reporting group values	Placebo	Total	
Number of subjects	17	193	
Age categorical Units: Subjects			

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

End points

End points reporting groups

Reporting group title	Naproxen Sodium/Caffeine 440/200 mg
Reporting group description:	
Subjects received 440 mg naproxen sodium and 200 mg caffeine after extraction of third molars	
Reporting group title	Naproxen Sodium/Caffeine 440/130 mg
Reporting group description:	
Subjects received 440 mg naproxen sodium and 130 mg caffeine after extraction of third molars	
Reporting group title	Naproxen Sodium/Caffeine 220/100 mg
Reporting group description:	
Subjects received 220 mg naproxen sodium and 100 mg caffeine after extraction of third molars	
Reporting group title	Naproxen Sodium/Caffeine 220/65 mg
Reporting group description:	
Subjects received 220 mg naproxen sodium and 65 mg caffeine after extraction of third molars	
Reporting group title	Naproxen Sodium 220 mg
Reporting group description:	
Subjects received 220 mg naproxen sodium after extraction of third molars	
Reporting group title	Caffeine 200 mg
Reporting group description:	
Subjects received 200 mg caffeine after extraction of third molars	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo after extraction of third molars	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All participants who were randomized and took at least one dose of investigational product. Safety measures were analyzed for all participants in the safety population	
Subject analysis set title	Per protocol set
Subject analysis set type	Per protocol
Subject analysis set description:	
Included all participants in the Safety Population who provided at least one pain assessment after the first dose of the investigational product and did not have any major protocol violations and completed the 12-hour assessments. PP population was used as the primary analysis for the efficacy parameters	

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

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

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics was provided. Inferential statistics is considered confidential at this point in time

End point values	Naproxen Sodium/Caffeine 440/200 mg	Naproxen Sodium/Caffeine 440/130 mg	Naproxen Sodium/Caffeine 220/100 mg	Naproxen Sodium/Caffeine 220/65 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	31	32	32
Units: Scores on a scale*hours				
arithmetic mean (standard deviation)				
SPID 0-8	35.45 (± 14.517)	37.87 (± 16.876)	30.70 (± 17.679)	36.02 (± 14.825)

End point values	Naproxen Sodium 220 mg	Caffeine 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	16	16	
Units: Scores on a scale*hours				
arithmetic mean (standard deviation)				
SPID 0-8	29.95 (± 19.067)	8.75 (± 21.465)	6.03 (± 17.810)	

Statistical analyses

No statistical analyses for this end point

Secondary: Total pain relief (TOTPAR) over 8 hours

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

End point description:

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

End point type	Secondary

End point timeframe:

Up to 8 hours post dose

End point values	Naproxen Sodium/Caffeine 440/200 mg	Naproxen Sodium/Caffeine 440/130 mg	Naproxen Sodium/Caffeine 220/100 mg	Naproxen Sodium/Caffeine 220/65 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	31	32	32
Units: Scores on a scale*hours				
arithmetic mean (standard deviation)				
TOTPAR 0-8	19.58 (± 7.007)	20.26 (± 7.673)	17.41 (± 8.063)	19.53 (± 6.448)

End point values	Naproxen Sodium 220 mg	Caffeine 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	16	16	
Units: Scores on a scale*hours				
arithmetic mean (standard deviation)				
TOTPAR 0-8	16.27 (± 8.514)	7.03 (± 9.283)	5.44 (± 7.709)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first use of rescue medication

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

End point values	Naproxen Sodium/Caffeine 440/200 mg	Naproxen Sodium/Caffeine 440/130 mg	Naproxen Sodium/Caffeine 220/100 mg	Naproxen Sodium/Caffeine 220/65 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	31	32	32
Units: hours				
median (inter-quartile range (Q1-Q3))	99999 (99999 to 99999)	99999 (8.967 to 99999)	99999 (8.817 to 99999)	99999 (99999 to 99999)

End point values	Naproxen Sodium 220 mg	Caffeine 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	16	16	
Units: hours				
median (inter-quartile range (Q1-Q3))	99999 (8.125 to 99999)	2.083 (1.275 to 99999)	2.125 (1.408 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: The cumulative percentage of subjects taking rescue medication

End point title	The cumulative percentage of subjects taking rescue medication

End point description:

End point type	Secondary

End point timeframe:

Up to 12 hours post dose

End point values	Naproxen Sodium/Caffeine 440/200 mg	Naproxen Sodium/Caffeine 440/130 mg	Naproxen Sodium/Caffeine 220/100 mg	Naproxen Sodium/Caffeine 220/65 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	31	32	32
Units: percent				
number (not applicable)				
0.5 Hours Post-Dose	0	0	0	0
1 Hour Post-Dose	0	0	0	0
1.5 Hours Post-Dose	0	3.2	3.1	0
2 Hours Post-Dose	0	3.2	3.1	0
3 Hours Post-Dose	0	6.5	6.3	3.1
4 Hours Post-Dose	3.1	6.5	9.4	3.1
5 Hours Post-Dose	9.4	6.5	15.6	3.1
6 Hours Post-Dose	9.4	9.7	18.8	6.3
7 Hours Post-Dose	12.5	9.7	21.9	6.3
8 Hours Post-Dose	15.6	9.7	21.9	9.4
9 Hours Post-Dose	21.9	25.8	25.0	9.4
10 Hours Post-Dose	25.0	25.8	28.1	15.6
11 Hours Post-Dose	25.0	25.8	28.1	15.6
12 Hours Post-Dose	25.0	29.0	28.1	18.8

End point values	Naproxen Sodium 220 mg	Caffeine 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	16	16	
Units: percent				
number (not applicable)				
0.5 Hours Post-Dose	0	0	0	
1 Hour Post-Dose	0	0	0	
1.5 Hours Post-Dose	0	37.5	25.0	
2 Hours Post-Dose	0	50	37.5	
3 Hours Post-Dose	15.6	56.3	56.3	
4 Hours Post-Dose	18.8	56.3	68.8	

5 Hours Post-Dose	18.8	62.5	68.8	
6 Hours Post-Dose	21.9	68.8	68.8	
7 Hours Post-Dose	21.9	68.8	68.8	
8 Hours Post-Dose	21.9	68.8	75.0	
9 Hours Post-Dose	28.1	68.8	75.0	
10 Hours Post-Dose	31.3	68.8	75.0	
11 Hours Post-Dose	34.4	68.8	75.0	
12 Hours Post-Dose	34.4	75.0	75.0	

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

End point values	Naproxen Sodium/Caffeine 440/200 mg	Naproxen Sodium/Caffeine 440/130 mg	Naproxen Sodium/Caffeine 220/100 mg	Naproxen Sodium/Caffeine 220/65 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	31	32	32
Units: Scores on a scale*hours				
arithmetic mean (standard deviation)				
SPID 0-2	8.30 (± 3.141)	8.68 (± 3.789)	7.17 (± 3.721)	6.92 (± 3.501)
SPID 0-4	18.02 (± 6.387)	19.26 (± 8.019)	15.58 (± 7.697)	17.05 (± 7.232)
SPID 0-12	50.58 (± 24.237)	52.45 (± 27.305)	44.80 (± 28.929)	52.45 (± 23.022)

End point values	Naproxen Sodium 220 mg	Caffeine 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	16	16	
Units: Scores on a scale*hours				

arithmetic mean (standard deviation)				
SPID 0-2	6.05 (± 3.511)	2.13 (± 4.060)	1.16 (± 2.925)	
SPID 0-4	14.33 (± 8.391)	4.50 (± 9.604)	2.59 (± 7.625)	
SPID 0-12	43.08 (± 30.034)	12.44 (± 32.059)	9.41 (± 28.162)	

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

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

End point values	Naproxen Sodium/Caffeine 440/200 mg	Naproxen Sodium/Caffeine 440/130 mg	Naproxen Sodium/Caffeine 220/100 mg	Naproxen Sodium/Caffeine 220/65 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	31	32	32
Units: Scores on a scale*hours				
arithmetic mean (standard deviation)				
TOTPAR 0-2	4.83 (± 1.401)	4.77 (± 1.731)	4.22 (± 1.596)	3.97 (± 1.436)
TOTPAR 0-4	10.27 (± 2.750)	10.29 (± 3.449)	8.84 (± 3.286)	9.28 (± 2.842)
TOTPAR 0-12	28.20 (± 12.262)	28.26 (± 12.690)	25.13 (± 13.291)	28.72 (± 10.678)

End point values	Naproxen Sodium 220 mg	Caffeine 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	16	16	
Units: Scores on a scale*hours				
arithmetic mean (standard deviation)				
TOTPAR 0-2	3.52 (± 1.644)	1.66 (± 1.767)	1.06 (± 1.328)	
TOTPAR 0-4	7.86 (± 3.813)	3.59 (± 4.148)	2.44 (± 3.281)	
TOTPAR 0-12	22.95 (± 13.206)	10.28 (± 13.882)	8.44 (± 12.419)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pain Intensity Difference (PID) at each evaluation

End point title	Pain Intensity Difference (PID) at each evaluation

End point description:

Pain intensity is measured using Numerical Rating Scale (from 0 to 10: 0 = no pain, 10 = worst possible pain). For each post dose time point, pain intensity difference (PID) is derived by subtracting the pain intensity at the post dose time point from the baseline intensity score (baseline score – post-baseline score). A positive difference is indicative of improvement

End point type	Secondary

End point timeframe:

Up to 12 hours post dose

End point values	Naproxen Sodium/Caffeine 440/200 mg	Naproxen Sodium/Caffeine 440/130 mg	Naproxen Sodium/Caffeine 220/100 mg	Naproxen Sodium/Caffeine 220/65 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	31	3	31
Units: Scores on a scale				
arithmetic mean (standard deviation)				
0.5 Hours Post-Dose	2.3 (± 2.07)	2.6 (± 1.82)	2.1 (± 2.23)	1.4 (± 1.56)
1 Hour Post-Dose	4.2 (± 1.88)	4.2 (± 2.44)	3.7 (± 1.95)	3.4 (± 2.39)
1.5 Hours Post-Dose	4.9 (± 1.67)	5.1 (± 2.26)	4.3 (± 1.98)	4.2 (± 2.32)
2 Hours Post-Dose	5.1 (± 1.76)	5.5 (± 2.20)	4.3 (± 2.23)	4.8 (± 2.23)
3 Hours Post-Dose	5.0 (± 1.82)	5.4 (± 2.27)	4.3 (± 2.33)	5.0 (± 2.29)
4 Hours Post-Dose	4.8 (± 2.17)	5.2 (± 2.59)	4.1 (± 2.62)	5.1 (± 2.27)
5 Hours Post-Dose	4.7 (± 2.28)	5.0 (± 2.42)	4.0 (± 2.72)	5.0 (± 2.25)
6 Hours Post-Dose	4.6 (± 2.24)	4.8 (± 2.42)	3.8 (± 2.87)	4.9 (± 2.40)
7 Hours Post-Dose	4.3 (± 2.55)	4.5 (± 2.45)	3.8 (± 3.07)	4.7 (± 2.31)
8 Hours Post-Dose	4.0 (± 2.53)	4.2 (± 2.65)	3.7 (± 3.12)	4.3 (± 2.29)
9 Hours Post-Dose	3.8 (± 2.71)	3.8 (± 3.12)	3.6 (± 3.00)	4.2 (± 2.45)
10 Hours Post-Dose	3.8 (± 2.88)	3.7 (± 3.04)	3.4 (± 3.15)	4.1 (± 2.60)
11 Hours Post-Dose	3.8 (± 2.92)	3.5 (± 3.02)	3.6 (± 3.17)	4.2 (± 2.79)
12 Hours Post-Dose	3.8 (± 2.97)	3.6 (± 3.06)	3.5 (± 3.38)	4.0 (± 2.92)

End point values	Naproxen Sodium 220 mg	Caffeine 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	16	16	

Units: Scores on a scale				
arithmetic mean (standard deviation)				
0.5 Hours Post-Dose	1.5 (± 1.34)	0.8 (± 0.98)	0.5 (± 0.89)	
1 Hour Post-Dose	2.9 (± 1.88)	1.2 (± 2.26)	0.6 (± 1.71)	
1.5 Hours Post-Dose	3.7 (± 2.16)	1.2 (± 2.79)	0.7 (± 1.74)	
2 Hours Post-Dose	4.1 (± 2.22)	1.1 (± 2.67)	0.5 (± 1.86)	
3 Hours Post-Dose	4.0 (± 2.83)	1.1 (± 2.85)	0.6 (± 2.42)	
4 Hours Post-Dose	4.3 (± 2.82)	1.3 (± 3.11)	0.9 (± 2.78)	
5 Hours Post-Dose	4.1 (± 2.83)	1.1 (± 3.14)	1.0 (± 2.92)	
6 Hours Post-Dose	3.9 (± 2.88)	1.1 (± 3.19)	1.0 (± 3.06)	
7 Hours Post-Dose	3.9 (± 3.08)	1.1 (± 3.36)	0.8 (± 2.49)	
8 Hours Post-Dose	3.7 (± 2.96)	0.9 (± 2.95)	0.7 (± 2.65)	
9 Hours Post-Dose	3.6 (± 3.14)	1.1 (± 3.09)	0.8 (± 2.74)	
10 Hours Post-Dose	3.3 (± 3.07)	1.1 (± 3.07)	0.9 (± 2.99)	
11 Hours Post-Dose	3.1 (± 3.02)	0.8 (± 2.99)	0.9 (± 2.96)	
12 Hours Post-Dose	3.1 (± 2.97)	0.8 (± 3.00)	0.9 (± 2.96)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pain relief score at each evaluation

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

End point values	Naproxen Sodium/Caffeine 440/200 mg	Naproxen Sodium/Caffeine 440/130 mg	Naproxen Sodium/Caffeine 220/100 mg	Naproxen Sodium/Caffeine 220/65 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	31	32	32
Units: Scores on a scale				
arithmetic mean (standard deviation)				
0.5 Hours Post-Dose	1.6 (± 1.08)	1.5 (± 0.89)	1.5 (± 1.02)	0.9 (± 0.80)
1 Hours Post-Dose	2.4 (± 0.84)	2.3 (± 1.22)	2.2 (± 0.91)	2.0 (± 1.14)
1.5 Hours Post-Dose	2.8 (± 0.64)	2.8 (± 0.99)	2.3 (± 0.87)	2.4 (± 0.91)
2 Hours Post-Dose	2.8 (± 0.85)	2.9 (± 1.01)	2.4 (± 1.01)	2.6 (± 0.79)
3 Hours Post-Dose	2.8 (± 0.79)	2.8 (± 0.97)	2.4 (± 1.04)	2.6 (± 0.91)
4 Hours Post-Dose	2.7 (± 1.07)	2.7 (± 1.19)	2.3 (± 1.16)	2.7 (± 0.96)
5 Hours Post-Dose	2.6 (± 1.16)	2.6 (± 1.15)	2.3 (± 1.27)	2.7 (± 1.00)
6 Hours Post-Dose	2.4 (± 1.16)	2.6 (± 1.18)	2.2 (± 1.35)	2.7 (± 1.10)
7 Hours Post-Dose	2.3 (± 1.34)	2.5 (± 1.15)	2.1 (± 1.38)	2.5 (± 1.08)
8 Hours Post-Dose	2.1 (± 1.33)	2.3 (± 1.28)	2.1 (± 1.46)	2.4 (± 1.19)

9 Hours Post-Dose	2.2 (± 1.40)	2.1 (± 1.48)	2.0 (± 1.45)	2.3 (± 1.12)
10 Hours Post-Dose	2.2 (± 1.51)	2.0 (± 1.43)	1.8 (± 1.42)	2.3 (± 1.28)
11 Hours Post-Dose	2.1 (± 1.52)	1.9 (± 1.40)	1.9 (± 1.48)	2.4 (± 1.34)
12 Hours Post-Dose	2.2 (± 1.55)	1.9 (± 1.46)	2.0 (± 1.51)	2.2 (± 1.45)

End point values	Naproxen Sodium 220 mg	Caffeine 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	16	16	
Units: Scores on a scale				
arithmetic mean (standard deviation)				
0.5 Hours Post-Dose	1.0 (± 0.74)	0.6 (± 0.62)	0.4 (± 0.63)	
1 Hours Post-Dose	1.8 (± 0.91)	0.9 (± 1.00)	0.6 (± 0.81)	
1.5 Hours Post-Dose	2.0 (± 1.05)	0.9 (± 1.24)	0.6 (± 0.73)	
2 Hours Post-Dose	2.2 (± 1.01)	0.8 (± 1.05)	0.5 (± 0.82)	
3 Hours Post-Dose	2.1 (± 1.21)	0.9 (± 1.24)	0.6 (± 1.09)	
4 Hours Post-Dose	2.2 (± 1.26)	1.0 (± 1.37)	0.8 (± 1.18)	
5 Hours Post-Dose	2.2 (± 1.24)	0.9 (± 1.36)	0.8 (± 1.18)	
6 Hours Post-Dose	2.1 (± 1.30)	0.9 (± 1.45)	0.8 (± 1.24)	
7 Hours Post-Dose	2.1 (± 1.29)	0.9 (± 1.50)	0.8 (± 1.28)	
8 Hours Post-Dose	2.0 (± 1.28)	0.8 (± 1.33)	0.7 (± 1.25)	
9 Hours Post-Dose	1.9 (± 1.41)	0.9 (± 1.36)	0.8 (± 1.34)	
10 Hours Post-Dose	1.8 (± 1.41)	0.9 (± 1.36)	0.8 (± 1.34)	
11 Hours Post-Dose	1.4 (± 1.32)	0.8 (± 1.34)	0.8 (± 1.34)	
12 Hours Post-Dose	1.6 (± 1.39)	0.8 (± 1.34)	0.8 (± 1.34)	

Statistical analyses

No statistical analyses for this end point

Secondary: Peak pain intensity difference (PID)

End point title	Peak pain intensity difference (PID)

End point description:

Pain intensity is measured using Numerical Rating Scale (from 0 to 10: 0 = no pain, 10 = worst possible pain). For each post dose time point, pain intensity difference (PID) is derived by subtracting the pain intensity at the post dose time point from the baseline intensity score (baseline score – post-baseline score)

End point type	Secondary

End point timeframe:

Up to 12 hours post dose

End point values	Naproxen Sodium/Caffeine 440/200 mg	Naproxen Sodium/Caffeine 440/130 mg	Naproxen Sodium/Caffeine 220/100 mg	Naproxen Sodium/Caffeine 220/65 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	31	32	32
Units: Scores on a scale				
arithmetic mean (standard deviation)	6.0 (± 1.53)	6.2 (± 1.97)	5.9 (± 2.01)	6.3 (± 1.72)

End point values	Naproxen Sodium 220 mg	Caffeine 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	16	16	
Units: Scores on a scale				
arithmetic mean (standard deviation)	5.3 (± 2.57)	2.7 (± 2.94)	2.3 (± 2.98)	

Statistical analyses

No statistical analyses for this end point

Secondary: Peak pain relief score

End point title	Peak pain relief score

End point description:

Pain relief is measured using Categorical Pain Relief Rating Scale (0 = No relief, 1 = a little relief, 2 = some relief, 3 = a lot of relief, 4 = complete relief)

End point type	Secondary

End point timeframe:

Up to 12 hours post dose

End point values	Naproxen Sodium/Caffeine 440/200 mg	Naproxen Sodium/Caffeine 440/130 mg	Naproxen Sodium/Caffeine 220/100 mg	Naproxen Sodium/Caffeine 220/65 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	31	32	32
Units: Scores on a scale				
arithmetic mean (standard deviation)	3.3 (± 0.62)	3.2 (± 0.78)	3.0 (± 0.82)	3.1 (± 0.66)

End point values	Naproxen Sodium 220 mg	Caffeine 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	16	16	
Units: Scores on a scale				
arithmetic mean (standard deviation)	2.6 (± 1.01)	1.6 (± 1.55)	1.3 (± 1.39)	

Statistical analyses

No statistical analyses for this end point

Secondary: Global assessment of the investigational product

End point title	Global assessment of the investigational product

End point description:

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

End point type	Secondary

End point timeframe:

Up to 12 hours post dose

End point values	Naproxen Sodium/Caffeine 440/200 mg	Naproxen Sodium/Caffeine 440/130 mg	Naproxen Sodium/Caffeine 220/100 mg	Naproxen Sodium/Caffeine 220/65 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	31	32	32
Units: Percentage of subjects				
number (not applicable)				
Poor (0)	3.1	3.2	3.1	3.1
Fair (1)	6.3	3.2	12.5	6.3
Good (2)	15.6	19.4	28.1	21.9
Very Good (3)	56.3	45.2	40.6	53.1
Excellent (4)	18.8	29.0	15.6	15.6

End point values	Naproxen Sodium 220 mg	Caffeine 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	16	16	
Units: Percentage of subjects				
number (not applicable)				
Poor (0)	12.5	50.6	62.5	
Fair (1)	15.6	6.3	12.5	
Good (2)	18.8	25.0	6.3	
Very Good (3)	43.8	12.5	18.8	
Excellent (4)	9.4	6.3	0.0	

Statistical analyses

No statistical analyses for this end point

Secondary: The number of subjects with adverse events

End point title	The number of subjects with adverse events

End point description:

End point type	Secondary

End point timeframe:

Up to 5 days post dose

End point values	Naproxen Sodium/Caffeine 440/200 mg	Naproxen Sodium/Caffeine 440/130 mg	Naproxen Sodium/Caffeine 220/100 mg	Naproxen Sodium/Caffeine 220/65 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	32	32	32
Units: Subjects	6	3	1	2

End point values	Naproxen Sodium 220 mg	Caffeine 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	16	17	
Units: Subjects	3	5	4	

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

End point type	Secondary

End point timeframe:

Up to 5 days post dose

End point values	Naproxen Sodium/Caffeine 440/200 mg	Naproxen Sodium/Caffeine 440/130 mg	Naproxen Sodium/Caffeine 220/100 mg	Naproxen Sodium/Caffeine 220/65 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	32	32	32
Units: Subjects	0	0	0	0

End point values	Naproxen Sodium 220 mg	Caffeine 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	16	17	
Units: Subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to 5 days post-dose	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1
Reporting groups	
Reporting group title	Naproxen Sodium/Caffeine 440/200 mg
Reporting group description: Participants received 440 mg naproxen sodium and 200 mg caffeine after randomization	
Reporting group title	Naproxen Sodium/Caffeine 440/130 mg
Reporting group description: Participants received 440 mg naproxen sodium and 130 mg caffeine after randomization	
Reporting group title	Naproxen Sodium/Caffeine 220/100 mg
Reporting group description: Participants received 220 mg naproxen sodium and 100 mg caffeine after randomization	
Reporting group title	Naproxen Sodium/Caffeine 220/65 mg
Reporting group description: Participants received 220 mg naproxen sodium and 65 mg caffeine after randomization	
Reporting group title	Naproxen Sodium 220 mg
Reporting group description: Participants received 220 mg naproxen sodium after randomization	
Reporting group title	Caffeine 200 mg
Reporting group description: Participants received 200 mg caffeine after randomization	
Reporting group title	Placebo
Reporting group description: Participants received matching placebo after randomization	

Serious adverse events	Naproxen Sodium/Caffeine 440/200 mg	Naproxen Sodium/Caffeine 440/130 mg	Naproxen Sodium/Caffeine 220/100 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 32 (0.00%)	0 / 32 (0.00%)	0 / 32 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Naproxen Sodium/Caffeine 220/65 mg	Naproxen Sodium 220 mg	Caffeine 200 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 32 (0.00%)	0 / 32 (0.00%)	0 / 16 (0.00%)

number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

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

Non-serious adverse events	Naproxen Sodium/Caffeine 440/200 mg	Naproxen Sodium/Caffeine 440/130 mg	Naproxen Sodium/Caffeine 220/100 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 32 (18.75%)	3 / 32 (9.38%)	1 / 32 (3.13%)
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 32 (3.13%)	1 / 32 (3.13%)	0 / 32 (0.00%)
occurrences (all)	1	1	0
Headache			
subjects affected / exposed	0 / 32 (0.00%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 32 (0.00%)	0 / 32 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Feeling hot			

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

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

Non-serious adverse events	Naproxen Sodium/Caffeine 220/65 mg	Naproxen Sodium 220 mg	Caffeine 200 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 32 (6.25%)	3 / 32 (9.38%)	5 / 16 (31.25%)
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	0 / 32 (0.00%)	0 / 32 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	2
Syncope			
subjects affected / exposed	0 / 32 (0.00%)	0 / 32 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 32 (0.00%)	0 / 32 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Feeling hot			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 32 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 32 (0.00%)	0 / 32 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Gastrointestinal disorders			

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

As non-key secondary endpoints "Time to first perceptible relief, first meaningful relief, first perceptible relief confirmed by meaningful relief" and "Cumulative percentage of subjects with at least '2-point PID' over time" were also analyzed.

Notes: