



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
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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
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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
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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
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Arm description:

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

Arm type	Experimental
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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	-
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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
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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
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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
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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
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End point description:

End point type	Secondary
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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
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End point description:

End point type	Secondary
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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
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End point description:

End point type	Secondary
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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)
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End point description:

End point type	Secondary
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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)
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End point description:

End point type	Secondary
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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'
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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
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End point description:

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

End point type	Secondary
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.0
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Reporting groups

Reporting group title	Fixed Dose Combination
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Reporting group description:

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

Reporting group title	Fixed Dose Combination
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Reporting group description:

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

Reporting group title	Placebo
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Reporting group description:

Placebo

Reporting group title	Caffeine
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Reporting group description:

Caffeine 100 mg

Reporting group title	Naproxen Sodium
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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			

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

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