Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled Trial to Compare the Duration of Analgesic Efficacy and Safety of Naproxen Sodium Tablets and Ibuprofen Tablets in Postsurgical Dental Pain

Summary

EudraCT number	2017-005049-67
Trial protocol	Outside EU/EEA
Global end of trial date	06 July 2018

Results information

Result version number	v1 (current)
This version publication date	06 January 2019
First version publication date	06 January 2019

Trial information

Trial identification

Sponsor protocol code	BAY117031/19762

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03404206
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 July 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the duration of analgesic efficacy as determined by the time to rescue medication of a single oral dose of naproxen sodium 440 mg (2 x 220 mg tablets) relative to ibuprofen 400 mg (2 x 200 mg tablets) and placebo (2 x tablets) over 24 hours in subjects experiencing moderate to severe post-impaction surgery dental pain.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 February 2018
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: 387
Worldwide total number of subjects	387
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)	110

Adults (18-64 years)	277
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at one center in the United States, between 12 February 2018 (first patient first visit) and 06 July 2018 (last patient last visit).

Pre-assignment

Screening details:

Overall, 387 subjects completed surgical teeth extraction, and all of them were randomized and received the treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Naproxen sodium (Aleve, BAY117031)

Arm description:

Subjects received one single dose of 440 mg naproxen sodium tablets (200 mg x 2 tablets, oral) after randomization

Arm type	Experimental
Investigational medicinal product name	Naproxen sodium (Aleve, BAY117031)
Investigational medicinal product code	BAY117031
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

220 mg x 2 tablets, oral, single dose

Arm title	Ibuprofen (Advil)

Arm description:

Subjects received one single dose of 400 mg ibuprofen tablets (200 mg x 2 tablets, oral) after randomization

Arm type	Active comparator
Investigational medicinal product name	Ibuprofen (Advil)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

200 mg x 2 tablets, oral, single dose

Arm title	Placebo

Arm description:

Subjects received one single dose of matching placebo tablets (2 tablets, oral) after randomization

Arm type	Placebo

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

Dosage and administration details:

Matching placebo, 2 tablets, oral, single dose

Number of subjects in period 1	Naproxen sodium (Aleve, BAY117031)	Ibuprofen (Advil)	Placebo
Started	166	166	55
Completed	162	164	55
Not completed	4	2	0
Consent withdrawn by subject	1	1	-
Lost to follow-up	3	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Naproxen sodium (Aleve, BAY117031)
Reporting group description:	
Subjects received one single dose of 440 mg naproxen sodium tablets (200 mg x 2 tablets, oral) after randomization	
Reporting group title	Ibuprofen (Advil)
Reporting group description:	
Subjects received one single dose of 400 mg ibuprofen tablets (200 mg x 2 tablets, oral) after randomization	
Reporting group title	Placebo
Reporting group description:	
Subjects received one single dose of matching placebo tablets (2 tablets, oral) after randomization	

Reporting group values	Naproxen sodium (Aleve, BAY117031)	Ibuprofen (Advil)	Placebo
Number of subjects	166	166	55
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	19.0	19.0	19.0
standard deviation	± 2.96	± 2.62	± 2.91
Gender categorical			
Units: Subjects			
Female	77	89	30
Male	89	77	25
Race			
Units: Subjects			
White	148	148	48
Black of African American	2	4	1
American Indian or Alaska Native	3	4	2
Asian	1	2	1
Native Hawaiian or Other Pacific Islander	1	3	1
Other	11	5	2
Ethnicity			
Units: Subjects			
Hispanic or Latino	23	25	10
Not Hispanic or Latino	143	141	45
Pain Intensity Score			
Categorical pain intensity scale - no pain (0), mild pain (1), moderate pain (2), or severe pain (3) was used for pain intensity assessments.			
Units: Subjects			
No Pain (0)	0	0	0
Mild Pain (1)	0	0	0
Moderate Pain (2)	69	67	23
Severe Pain (3)	97	99	32

Reporting group values	Total		
Number of subjects	387		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	196		
Male	191		
Race Units: Subjects			
White	344		
Black of African American	7		
American Indian or Alaska Native	9		
Asian	4		
Native Hawaiian or Other Pacific Islander	5		
Other	18		
Ethnicity Units: Subjects			
Hispanic or Latino	58		
Not Hispanic or Latino	329		
Pain Intensity Score			
Categorical pain intensity scale - no pain (0), mild pain (1), moderate pain (2), or severe pain (3) was used for pain intensity assessments.			
Units: Subjects			
No Pain (0)	0		
Mild Pain (1)	0		
Moderate Pain (2)	159		
Severe Pain (3)	228		

End points

End points reporting groups

Reporting group title	Naproxen sodium (Aleve, BAY117031)
Reporting group description:	
Subjects received one single dose of 440 mg naproxen sodium tablets (200 mg x 2 tablets, oral) after randomization	
Reporting group title	Ibuprofen (Advil)
Reporting group description:	
Subjects received one single dose of 400 mg ibuprofen tablets (200 mg x 2 tablets, oral) after randomization	
Reporting group title	Placebo
Reporting group description:	
Subjects received one single dose of matching placebo tablets (2 tablets, oral) after randomization	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
Included all subjects who were randomized and took at least one dose of investigational product	
Subject analysis set title	Intent-to-Treat (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Included all subjects in the Safety Population who provided at least one pain assessment after the first dose of the investigational product	
Subject analysis set title	Per-Protocol (PP) Population
Subject analysis set type	Per protocol
Subject analysis set description:	
Include all subjects in ITT who did not have any major protocol violations	

Primary: Time to first use of rescue medication

End point title	Time to first use of rescue medication
End point description:	
Time to first use of rescue medication was estimated using Kaplan-Meier method. If a subject did not take the rescue medication during the treatment period, (s)he was censored at the time of last assessment. "99999" denote that value could not be estimated due to censored data.	
End point type	Primary
End point timeframe:	
Up to 24 hours	

End point values	Naproxen sodium (Aleve, BAY117031)	Ibuprofen (Advil)	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	166[1]	165[2]	54[3]	
Units: hours				
number (not applicable)				
Minimum	1.22	1.22	1.18	
25th Percentile	11.017	8.267	2.117	
50th Percentile	99999	10.533	2.533	
75th Percentile	99999	14.117	12.100	
Maximum	22.17	18.28	21.75	

Notes:
[1] - Per-protocol population
[2] - Per-protocol population
[3] - Per-protocol population

Statistical analyses

Statistical analysis title	Time to first use of rescue medication
Comparison groups	Naproxen sodium (Aleve, BAY117031) v Ibuprofen (Advil)
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Logrank

Statistical analysis title	Time to first use of rescue medication
Comparison groups	Naproxen sodium (Aleve, BAY117031) v Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Logrank

Secondary: Sum of Pain Intensity Difference (SPID)

End point title	Sum of Pain Intensity Difference (SPID)

End point description:

Pain intensity was measured using Numerical Rating Scale (from 0 to 10: 0 = no pain, 10 = worst possible pain). For each postdose time point, pain intensity differences (PIDs) were derived by subtracting the pain intensity at the postdose time point from the baseline intensity score (baseline score – post-baseline score). A positive difference was indicative of improvement. Time-weighted sum of pain intensity differences (SPIDs) were calculated by multiplying the PID score at each postdose time point by the duration (in hours) since the preceding time point and then summing these values.

End point type	Secondary

End point timeframe:

Up to 24 hours

End point values	Naproxen sodium (Aleve, BAY117031)	Ibuprofen (Advil)	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	166[4]	165[5]	54[6]	
Units: Scores on a scale * hours				
arithmetic mean (standard deviation)	83.29 (± 57.177)	48.54 (± 40.705)	9.96 (± 58.197)	

Notes:
[4] - Per-protocol population
[5] - Per-protocol population
[6] - Per-protocol population

Statistical analyses

Statistical analysis title	Sum of Pain Intensity Difference (SPID)
Comparison groups	Naproxen sodium (Aleve, BAY117031) v Ibuprofen (Advil)
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Least squares means
Point estimate	-34.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-45.67
upper limit	-23.8

Statistical analysis title	Sum of Pain Intensity Difference (SPID)
Comparison groups	Placebo v Naproxen sodium (Aleve, BAY117031)
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Least squares means
Point estimate	-73.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-89.01
upper limit	-57.85

Statistical analysis title	Sum of Pain Intensity Difference (SPID)
Comparison groups	Ibuprofen (Advil) v Placebo
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Least squares means
Point estimate	-38.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-54.29
upper limit	-23.11

Secondary: Total Pain Relief (TOTPAR)

End point title	Total Pain Relief (TOTPAR)

End point description:

Pain relief was measured using Categorical Pain Relief Rating Scale (0 = No relief, 1 = a little relief, 2 = some relief, 3 = a lot of relief, 4 = complete relief). Total pain relief scores (TOTPARs) were calculated by multiplying the pain relief score at each postdose time point by the duration (in hours) since the preceding time point and then summing these values.

End point type	Secondary

End point timeframe:

Up to 24 hours

End point values	Naproxen sodium (Aleve, BAY117031)	Ibuprofen (Advil)	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	166[7]	165[8]	54[9]	
Units: Scores on a scale * hours				
arithmetic mean (standard deviation)	47.16 (± 28.228)	28.96 (± 21.097)	13.40 (± 23.328)	

Notes:

[7] - Per-protocol population

[8] - Per-protocol population

[9] - Per-protocol population

Statistical analyses

Statistical analysis title	Total Pain Relief (TOTPAR)
Comparison groups	Naproxen sodium (Aleve, BAY117031) v Ibuprofen (Advil)
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Least squares means
Point estimate	-18.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.52
upper limit	-12.89

Statistical analysis title	Total Pain Relief (TOTPAR)
Comparison groups	Naproxen sodium (Aleve, BAY117031) v Placebo
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Least squares means
Point estimate	-33.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.29
upper limit	-26.14

Statistical analysis title	Total Pain Relief (TOTPAR)
Comparison groups	Ibuprofen (Advil) v Placebo
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Least squares means
Point estimate	-15.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.09
upper limit	-7.93

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of study drug up to 10 days after the administration of study drug	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1
Reporting groups	
Reporting group title	Naproxen sodium (Aleve, BAY117031)
Reporting group description:	
Subjects received one single dose of 440 mg naproxen sodium tablets (200 mg x 2 tablets, oral) after randomization	
Reporting group title	Placebo
Reporting group description:	
Subjects received one single dose of matching placebo tablets (2 tablets, oral) after randomization	
Reporting group title	Ibuprofen (Advil)
Reporting group description:	
Subjects received one single dose of 400 mg ibuprofen tablets (200 mg x 2 tablets, oral) after randomization	

Serious adverse events	Naproxen sodium (Aleve, BAY117031)	Placebo	Ibuprofen (Advil)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 166 (0.60%)	0 / 55 (0.00%)	0 / 166 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 55 (0.00%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Naproxen sodium (Aleve, BAY117031)	Placebo	Ibuprofen (Advil)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 166 (15.06%)	16 / 55 (29.09%)	31 / 166 (18.67%)
Injury, poisoning and procedural complications			

Incision site pain			
subjects affected / exposed	1 / 166 (0.60%)	0 / 55 (0.00%)	0 / 166 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 166 (2.41%)	1 / 55 (1.82%)	5 / 166 (3.01%)
occurrences (all)	5	1	5
Headache			
subjects affected / exposed	3 / 166 (1.81%)	7 / 55 (12.73%)	6 / 166 (3.61%)
occurrences (all)	3	7	6
Paraesthesia			
subjects affected / exposed	0 / 166 (0.00%)	0 / 55 (0.00%)	1 / 166 (0.60%)
occurrences (all)	0	0	1
Tremor			
subjects affected / exposed	0 / 166 (0.00%)	0 / 55 (0.00%)	1 / 166 (0.60%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 166 (0.00%)	1 / 55 (1.82%)	1 / 166 (0.60%)
occurrences (all)	0	1	1
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 166 (0.00%)	0 / 55 (0.00%)	1 / 166 (0.60%)
occurrences (all)	0	0	1
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 166 (0.00%)	0 / 55 (0.00%)	1 / 166 (0.60%)
occurrences (all)	0	0	1
Eye disorders			
Eye pain			
subjects affected / exposed	1 / 166 (0.60%)	0 / 55 (0.00%)	0 / 166 (0.00%)
occurrences (all)	1	0	0
Eye swelling			
subjects affected / exposed	0 / 166 (0.00%)	0 / 55 (0.00%)	1 / 166 (0.60%)
occurrences (all)	0	0	1
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 166 (0.60%)	0 / 55 (0.00%)	0 / 166 (0.00%)
occurrences (all)	1	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 166 (0.00%)	1 / 55 (1.82%)	0 / 166 (0.00%)
occurrences (all)	0	1	0
Aphthous ulcer			
subjects affected / exposed	1 / 166 (0.60%)	0 / 55 (0.00%)	1 / 166 (0.60%)
occurrences (all)	1	0	1
Breath odour			
subjects affected / exposed	1 / 166 (0.60%)	0 / 55 (0.00%)	0 / 166 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	0 / 166 (0.00%)	1 / 55 (1.82%)	0 / 166 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	9 / 166 (5.42%)	11 / 55 (20.00%)	17 / 166 (10.24%)
occurrences (all)	10	12	20
Paraesthesia oral			
subjects affected / exposed	1 / 166 (0.60%)	0 / 55 (0.00%)	0 / 166 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	1 / 166 (0.60%)	7 / 55 (12.73%)	7 / 166 (4.22%)
occurrences (all)	1	10	9
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 55 (0.00%)	1 / 166 (0.60%)
occurrences (all)	1	0	1
Oropharyngeal pain			
subjects affected / exposed	2 / 166 (1.20%)	0 / 55 (0.00%)	0 / 166 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 166 (0.00%)	0 / 55 (0.00%)	1 / 166 (0.60%)
occurrences (all)	0	0	1
Psychiatric disorders			

Nervousness			
subjects affected / exposed	0 / 166 (0.00%)	0 / 55 (0.00%)	1 / 166 (0.60%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 166 (0.00%)	1 / 55 (1.82%)	0 / 166 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Alveolar osteitis			
subjects affected / exposed	4 / 166 (2.41%)	0 / 55 (0.00%)	1 / 166 (0.60%)
occurrences (all)	4	0	1
Ear infection			
subjects affected / exposed	0 / 166 (0.00%)	0 / 55 (0.00%)	1 / 166 (0.60%)
occurrences (all)	0	0	1
Periodontitis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 55 (0.00%)	0 / 166 (0.00%)
occurrences (all)	1	0	0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 166 (0.00%)	0 / 55 (0.00%)	1 / 166 (0.60%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 166 (0.60%)	0 / 55 (0.00%)	1 / 166 (0.60%)
occurrences (all)	1	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 January 2018	Clarified the details in inclusion, exclution and withdrawal criteria; Specified fasting time period during the surgery and study drug administration; Updated the timeline for restriction on concomitant therapy and smoking; Updated the starting timepoint for scheduled surgery from 0700 h to 0630 h; Removed saliva alcohol test; Removed the requirement of mandatory use of vasoconstrictor during surgery; Allowed the use of ice following the use of rescue medication.
15 February 2018	Modified the inclusion criterion to expand the permitted modified Demirjian root classification stage.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported