Clinical trial results:
Placebo-controlled, double-blind evaluation of the efficacy and safety of ibuprofen 5% topical gel for the treatment of ankle sprain

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2015-001874-16
Trial protocol	Outside EU/EEA
Global end of trial date	19 February 2015

Results information

Result version number	v1 (current)
This version publication date	23 July 2016
First version publication date	23 July 2016

Trial information

Trial identification

Sponsor protocol code	B3491009

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01945034
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Clinical Trials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.govCallCenter@pfizer.com
Scientific contact	Clinical Trials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.govCallCenter@pfizer.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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 July 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of Ibuprofen (IBU) 5 percent (%) Topical Gel versus topical placebo for the relief of pain associated with a first or second degree ankle sprain. Both twice a day (BID) and thrice a day (TID) dosing will be studied to determine the optimum dosing regimen (TID dosing vs. BID dosing).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and incompliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 November 2013
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: 304
Worldwide total number of subjects	304
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)	39
Adults (18-64 years)	260
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted in United States from 08 November 2013 to 19 February 2015.

Pre-assignment

Screening details:

Out of the 348 screened subjects, 304 were randomized and received treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ibuprofen Twice Daily

Arm description:

Ibuprofen 5 percent (%) topical gel twice daily was applied topically as a 4-inch strip approximately every 12 hours, for the first 7 days. Subsequently, on Days 8 through 10, subjects were permitted to use the study medication on an optional basis, according to the assigned dosing regimen.

Arm type	Experimental
Investigational medicinal product name	Ibuprofen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

Subject received Ibuprofen 5% topical gel twice daily topically as a 4-inch strip approximately every 12 hours, for the first 7 days.

Arm title	Ibuprofen Thrice Daily

Arm description:

Ibuprofen 5% Topical Gel thrice a day was applied topically as a 4-inch strip approximately every 6 hours, for the first 7 days. Subsequently, on Days 8 through 10, subjects were permitted to use the study medication on an optional basis, according to the assigned dosing regimen.

Arm type	Experimental
Investigational medicinal product name	Ibuprofen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

Subject received Ibuprofen 5% Topical Gel thrice a day topically as a 4-inch strip approximately every 6 hours, for the first 7 days.

Arm title	Placebo Combined

Arm description:

Placebo matched to Ibuprofen twice daily or thrice daily regimen was applied for first 7 days.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

Subjects administered with Placebo matched to Ibuprofen twice daily or thrice daily regimen for the first 7 days.

Number of subjects in period 1	Ibuprofen Twice Daily	Ibuprofen Thrice Daily	Placebo Combined
Started	67	85	152
Completed	66	80	145
Not completed	1	5	7
Consent withdrawn by subject	-	3	1
Unspecified	-	1	3
Medication Error	-	1	-
Lost to follow-up	-	-	2
Protocol deviation	1	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Ibuprofen Twice Daily
Reporting group description:	
Ibuprofen 5 percent (%) topical gel twice daily was applied topically as a 4-inch strip approximately every 12 hours, for the first 7 days. Subsequently, on Days 8 through 10, subjects were permitted to use the study medication on an optional basis, according to the assigned dosing regimen.	
Reporting group title	Ibuprofen Thrice Daily
Reporting group description:	
Ibuprofen 5% Topical Gel thrice a day was applied topically as a 4-inch strip approximately every 6 hours, for the first 7 days. Subsequently, on Days 8 through 10, subjects were permitted to use the study medication on an optional basis, according to the assigned dosing regimen.	
Reporting group title	Placebo Combined
Reporting group description:	
Placebo matched to Ibuprofen twice daily or thrice daily regimen was applied for first 7 days.	

Reporting group values	Ibuprofen Twice Daily	Ibuprofen Thrice Daily	Placebo Combined
Number of subjects	67	85	152
Age categorical Units: Subjects			
Adolescents (12-17 years)	16	5	18
Adults (18-64 years)	50	78	132
Elderly (From 65-84 years)	1	2	2
Age Continuous | Units: years			
arithmetic mean	31.7	35.2	33
standard deviation	± 15.2	± 14.72	± 13.9
Gender, Male/Female Units: participants			
Female	34	39	61
Male	33	46	91
Categorical Pain Severity Rating (PSR)			
Subjects were assessed by 4-Point category pain severity rating scale. Subjects rated their pain upon weight bearing using a four-point scale, as follows: 0 = None, 1 = Mild, 2 = Moderate, 3 = Severe. All Subjects had moderate or severe ankle pain upon weight bearing at baseline.			
Units: Subjects			
Moderate	43	63	102
Severe	24	22	50
Baseline Subject's Global Assessment of Ankle Injury			
Subjects were asked the following question: "Considering all the ways your ankle injury affects you, how are you doing today?" The subject's response was recorded using a 5-point scale: 1 = Very Good, No symptoms and no limitations of normal activities; 2 = Good, Mild symptoms and no limitation of normal activities; 3 = Fair, Moderate symptoms and limitations of some normal activities; 4 = Poor, Severe symptoms and inability to carry out most normal activities; and 5 = Very Poor, Very severe symptoms which are intolerable and inability to carry out all normal activities.			
Units: Subjects			
Very Good(1)	0	0	0
Good(2)	0	0	7
Fair(3)	34	56	77
Poor(4)	30	25	55

Very Poor(5)	3	4	13
Baseline Physician Global Assessment of Ankle Injury			
The physician assessment of the severity of the ankle injury was based on the subject's individual signs and symptoms which included pain, swelling, tenderness and limitation of range of movement, and graded using the following 6-point scale: 0 = Normal, No signs or symptoms; 1= Very mild, Very mild signs and symptoms; 2 = Mild, Mild signs and symptoms; 3 = Moderate, Moderate signs and symptoms; 4 = Severe, Severe signs and symptoms; 5 = Very severe, Very severe signs and symptoms.			
Units: Subjects			
Normal(0)	0	0	0
Very mild(1)	0	0	1
Mild(2)	9	28	30
Moderate(3)	50	54	101
Severe(4)	8	3	20
Very severe(5)	0	0	0
Baseline Subject Assessment of Normal Function/Activity			
Subjects were asked the following question: "How does your ankle injury affect your walking and normal activity?" The Subject's response was recorded using a 5-point scale: 1 = Normal activity and no pain; 2 = Normal activity with pain; 3 = Mildly restricted walking due to pain and can't resume normal activities; 4 = Moderately restricted walking due to pain and can't resume normal activities; 5 = Severely restricted walking due to pain and can't resume normal activities. The score ranges from 1-5, with higher scores indicates restricted activity.			
Units: Subjects			
Normal walking/activity and no pain (1)	0	0	0
Normal walking/activity with pain (2)	1	4	9
Mild restrict walking(3)	16	26	26
Moderate restrict walking(4)	43	45	91
Severe restrict walking(5)	7	10	26
Study Specific Characteristic |			
Units: Units on a scale			
arithmetic mean	8.3	8.1	8.4
standard deviation	± 1.25	± 1.13	± 1.17
Study Specific Characteristic |			
Units: Units on a scale			
arithmetic mean	6.2	6.5	6.5
standard deviation	± 1.77	± 1.48	± 1.7

Reporting group values	Total		
Number of subjects	304		
Age categorical			
Units: Subjects			
Adolescents (12-17 years)	39		
Adults (18-64 years)	260		
Elderly (From 65-84 years)	5		
Age Continuous |			
Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Units: participants			
Female	134		
Male	170		

Categorical Pain Severity Rating (PSR)			
Subjects were assessed by 4-Point category pain severity rating scale. Subjects rated their pain upon weight bearing using a four-point scale, as follows: 0 = None, 1 = Mild, 2 = Moderate, 3 = Severe. All Subjects had moderate or severe ankle pain upon weight bearing at baseline.			
Units: Subjects			
Moderate	208		
Severe	96		
Baseline Subject's Global Assessment of Ankle Injury			
Subjects were asked the following question: "Considering all the ways your ankle injury affects you, how are you doing today?" The subject's response was recorded using a 5-point scale: 1 = Very Good, No symptoms and no limitations of normal activities; 2 = Good, Mild symptoms and no limitation of normal activities; 3 = Fair, Moderate symptoms and limitations of some normal activities; 4 = Poor, Severe symptoms and inability to carry out most normal activities; and 5 = Very Poor, Very severe symptoms which are intolerable and inability to carry out all normal activities.			
Units: Subjects			
Very Good(1)	0		
Good(2)	7		
Fair(3)	167		
Poor(4)	110		
Very Poor(5)	20		
Baseline Physician Global Assessment of Ankle Injury			
The physician assessment of the severity of the ankle injury was based on the subject's individual signs and symptoms which included pain, swelling, tenderness and limitation of range of movement, and graded using the following 6-point scale: 0 = Normal, No signs or symptoms; 1= Very mild, Very mild signs and symptoms; 2 = Mild, Mild signs and symptoms; 3 = Moderate, Moderate signs and symptoms; 4 = Severe, Severe signs and symptoms; 5 = Very severe, Very severe signs and symptoms.			
Units: Subjects			
Normal(0)	0		
Very mild(1)	1		
Mild(2)	67		
Moderate(3)	205		
Severe(4)	31		
Very severe(5)	0		
Baseline Subject Assessment of Normal Function/Activity			
Subjects were asked the following question: "How does your ankle injury affect your walking and normal activity?" The Subject's response was recorded using a 5-point scale: 1 = Normal activity and no pain; 2 = Normal activity with pain; 3 = Mildly restricted walking due to pain and can't resume normal activities; 4 = Moderately restricted walking due to pain and can't resume normal activities; 5 = Severely restricted walking due to pain and can't resume normal activities. The score ranges from 1-5, with higher scores indicates restricted activity.			
Units: Subjects			
Normal walking/activity and no pain (1)	0		
Normal walking/activity with pain (2)	14		
Mild restrict walking(3)	68		
Moderate restrict walking(4)	179		
Severe restrict walking(5)	43		
Study Specific Characteristic |			
Units: Units on a scale			
arithmetic mean			
standard deviation	-		
Study Specific Characteristic |			
Units: Units on a scale			
arithmetic mean			

standard deviation	-		

End points

End points reporting groups

Reporting group title	Ibuprofen Twice Daily
Reporting group description:	
Ibuprofen 5 percent (%) topical gel twice daily was applied topically as a 4-inch strip approximately every 12 hours, for the first 7 days. Subsequently, on Days 8 through 10, subjects were permitted to use the study medication on an optional basis, according to the assigned dosing regimen.	
Reporting group title	Ibuprofen Thrice Daily
Reporting group description:	
Ibuprofen 5% Topical Gel thrice a day was applied topically as a 4-inch strip approximately every 6 hours, for the first 7 days. Subsequently, on Days 8 through 10, subjects were permitted to use the study medication on an optional basis, according to the assigned dosing regimen.	
Reporting group title	Placebo Combined
Reporting group description:	
Placebo matched to Ibuprofen twice daily or thrice daily regimen was applied for first 7 days.	

Primary: Sum of Pain Intensity Difference (SPID) on Weight Bearing Over 3 Days (SPID WB0-3)

End point title	Sum of Pain Intensity Difference (SPID) on Weight Bearing Over 3 Days (SPID WB0-3)
End point description:	
PI was assessed on an 11-point numerical rating scale from 0=no pain to 10=most severe pain. Pain intensity difference (PID) was the difference between baseline PI (prior to the first dose) and current PI at assessment. SPID was calculated as the time-weighted sum of PID scores over 3 days (72 hours). Total score ranges from -360 (higher pain relief) to 432 (lower pain relief) for SPID WB0-3. SPID is a value of change from baseline and as pain score at base line is usually higher than that at post baseline, a negative value of SPID indicates higher pain relief from baseline. The full analysis set included all randomized subjects who dosed with the study medication and provided a baseline assessment.	
End point type	Primary
End point timeframe:	
Over 3 Days (0-72 hours)	

End point values	Ibuprofen Twice Daily	Ibuprofen Thrice Daily	Placebo Combined	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	85	152	
Units: units on a scale				
least squares mean (standard error)	188.9 (± 14.81)	173.6 (± 13.6)	165.9 (± 10.34)	

Statistical analyses

Statistical analysis title	SPIDWB 0-3:Ibuprofen Twice DailyvsPlacebo Combined

Statistical analysis description:

The analysis of variance (ANOVA) model was used which contains treatment, baseline categorical pain severity rating, pooled site blocks, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19 [1]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.49
upper limit	57.56

Notes:

[1] - p-value <=0.05 for treatment effects

Statistical analysis title	SPIDWB0-3:Ibuprofen Thrice DailyvsPlacebo Combined

Statistical analysis description:

The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site blocks, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.633 [2]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	7.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.2
upper limit	39.7

Notes:

[2] - p-value <=0.05 for treatment effects

Statistical analysis title	SPIDWB0-3:Ibuprofen Twice DailyvsThrice Daily

Statistical analysis description:

The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site blocks, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.436 [3]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-15.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-53.87
upper limit	23.3

Notes:

[3] - p-value <=0.05 for treatment effects

Primary: Sum of Ankle Pain Intensity Difference on Weight Bearing Over 24 Hours After Dose 1 (SPID WB24)

End point title	Sum of Ankle Pain Intensity Difference on Weight Bearing Over 24 Hours After Dose 1 (SPID WB24)

End point description:

PI was assessed on an 11-point numerical rating scale from 0=no pain to 10=most severe pain. PID was the difference between baseline PI (prior to the first dose) and current PI at assessment. SPID was calculated as the time-weighted sum of PID scores over 24 hours. Total score ranges from -120 (higher pain relief) to 144 (lower pain relief) for SPID WB24. SPID is a value of change from baseline. Pain score at base line is usually higher than that at post baseline. So negative value of SPID indicates pain relief from baseline, while a positive value means a worst pain comparing to baseline, a negative value of SPID indicates higher pain relief from baseline, a negative value of SPID indicates higher pain relief from baseline. The full analysis set included all randomized subjects who dosed with the study medication and provided a baseline assessment.

End point type	Primary

End point timeframe:

0 to 24 hours

End point values	Ibuprofen Twice Daily	Ibuprofen Thrice Daily	Placebo Combined	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	85	152	
Units: units on a scale				
least squares mean (standard error)	46.9 (± 5.03)	41.1 (± 4.62)	42.1 (± 3.51)	

Statistical analyses

Statistical analysis title	SPIDWB24:Ibuprofen Twice DailyvsPlacebo Combined

Statistical analysis description:

The ANOVA model was used which contains treatment, baseline categorical pain severity rating (BLPSR), pooled site blocks, and baseline pain intensity on weight bearing (BLPIWB) terms. 95% CI not includes 0 for treatment effect. Upper limit of 95% CI< 0 for Ibuprofen treatment significantly better than combined Placebo. Comparison: tested at the 0.05 level of significance (2-sided). A comparison was eligible for being declared significant only if preceding comparison was significant.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.426 [4]
Method	ANOVA
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	4.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.98
upper limit	16.49

Notes:

[4] - p-value <=0.05 for treatment effects

Statistical analysis title	SPIDWB24:Ibuprofen Thrice DailyvsPlacebo Combined

Statistical analysis description:

The ANOVA model was used which contains treatment, BLPSR, pooled site blocks, and BLPIWB terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo. Comparison: tested at the 0.05 level of significance (2-sided). A comparison was eligible for being declared significant only if preceding comparison was significant.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.85 [5]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.9
upper limit	9.82

Notes:

[5] - p-value <=0.05 for treatment effects

Statistical analysis title	SPIDWB24:Ibuprofen Twice DailyvsThrice Daily

Statistical analysis description:

The ANOVA model was used which contains treatment, BLPSR, pooled site blocks, and BLPIWB terms. A comparison was eligible for being declared significant only if preceding comparison was significant.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.385 [6]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-5.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.91
upper limit	7.32

Notes:

[6] - p-value <=0.05 for treatment effects

Secondary: Sum of Pain Intensity Difference at Rest Over 24 Hours on Day 1 (SPID

R24)	
End point title	Sum of Pain Intensity Difference at Rest Over 24 Hours on Day 1 (SPID R24)

End point description:

PI was assessed on an 11-point numerical rating scale from 0=no pain to 10=most severe pain. PID was the difference between baseline PI (prior to the first dose) and current PI at assessment. SPID was calculated as the time-weighted sum of PID scores over 24 hours. Total score ranges from -240 (higher pain relief) to 96 (lower pain relief) for SPID at rest. SPID is a value of change from baseline. Pain score at base line is usually higher than that at post baseline. So negative value of SPID indicates pain relief from baseline, while positive value means a worst pain comparing to baseline, a negative value of SPID indicates higher pain relief from baseline. The full analysis set included all randomized subjects who dosed with the study medication and provided a baseline assessment.

End point type	Secondary

End point timeframe:

0 to 24 hours

End point values	Ibuprofen Twice Daily	Ibuprofen Thrice Daily	Placebo Combined	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	85	152	
Units: units on a scale				
least squares mean (standard error)	44.7 (± 4.65)	29.4 (± 4.29)	34.7 (± 3.22)	

Statistical analyses

Statistical analysis title	SPIDR24:Ibuprofen Twice DailyvsPlacebo Combined

Statistical analysis description:

The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site blocks, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.072 [7]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	10
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.92
upper limit	20.91

Notes:

[7] - p-value <=0.05 for treatment effects

Statistical analysis title	SPIDR24:Ibuprofen Thrice DailyvsPlacebo Combined

Statistical analysis description:

The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled

site blocks, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.296 [8]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-5.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.4
upper limit	4.7

Notes:

[8] - p-value <=0.05 for treatment effects

Statistical analysis title	SPID R24: Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site blocks, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.014 [9]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-15.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.53
upper limit	-3.16

Notes:

[9] - p-value <=0.05 for treatment effects

Secondary: Change From Baseline in Subject’s Global Assessment of Ankle Injury at Day 3 and 10

End point title	Change From Baseline in Subject’s Global Assessment of Ankle Injury at Day 3 and 10

End point description:

Subject’s global assessments of ankle injury was measured using 5-point scale: 1= Very Good (No symptoms and no limitations of normal activities), 2= Good (Mild symptoms and no limitation of normal activities), 3= Fair (Moderate symptoms and limitations of some normal activities), 4= Poor (Severe symptoms and inability to carry out most normal activities), 5= Very Poor (Very severe symptoms which are intolerable and inability to carry out all normal activities). The full analysis set included all randomized subjects who dosed with the study medication and provided a baseline assessment.

End point type	Secondary

End point timeframe:

Baseline, Day 3, 10

End point values	Ibuprofen Twice Daily	Ibuprofen Thrice Daily	Placebo Combined	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	85	152	
Units: units on a scale				
least squares mean (standard error)				
Change at: Day 3	0.7 (± 0.09)	0.7 (± 0.08)	0.6 (± 0.06)	
Change at: Day 10	1.8 (± 0.09)	1.7 (± 0.09)	1.6 (± 0.07)	

Statistical analyses

Statistical analysis title	Day 3: Ibuprofen Twice Daily vs Placebo Combined

Statistical analysis description:

Day 3: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline subject global assessment terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.305 [10]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.3

Notes:

[10] - p-value <=0.05 for treatment effects

Statistical analysis title	Day 3: Ibuprofen Thrice Daily vs Placebo Combined

Statistical analysis description:

Day 3: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline subject global assessment terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.261 [11]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.29

Notes:

[11] - p-value <=0.05 for treatment effects

Statistical analysis title	Day 3: Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Day 3: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline subject global assessment terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.996 [12]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	0.22

Notes:

[12] - p-value <=0.05 for treatment effects

Statistical analysis title	Day 10: Ibuprofen Twice Daily vs Placebo Combined

Statistical analysis description:

Day 10: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline subject global assessment terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.21 [13]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.36

Notes:

[13] - p-value <=0.05 for treatment effects

Statistical analysis title	Day 10: Ibuprofen Thrice Daily vs Placebo Combined

Statistical analysis description:

Day 10: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline subject global assessment terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.556 [14]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.27

Notes:

[14] - p-value <=0.05 for treatment effects

Statistical analysis title	Day 10: Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Day 10: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline subject global assessment terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.534 [15]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	0.17

Notes:

[15] - p-value <=0.05 for treatment effects

Secondary: Change From Baseline in Physician Global Assessment of Ankle Injury at Day 3 and 10

End point title	Change From Baseline in Physician Global Assessment of Ankle Injury at Day 3 and 10

End point description:

The physician assessment of the severity of the ankle injury was based on the subject's individual signs and symptoms which included pain, swelling, tenderness and limitation of range of movement, and was measured using 6-point scale: 0= Normal (No signs or symptoms) , 1= Very mild (Very mild signs and symptoms), 2= Mild (Mild signs and symptoms), 3= Moderate (Moderate signs and symptoms), 4= Severe (Severe signs and symptoms), 5= Very severe (Very severe signs and symptoms). A higher score is indicative of lesser improvement. Change from baseline was calculated as baseline value minus post-treatment value. The full analysis set included all randomized subjects who dosed with the study medication and provided a baseline assessment.

End point type	Secondary

End point timeframe:
Baseline, Day 3, 10

End point values	Ibuprofen Twice Daily	Ibuprofen Thrice Daily	Placebo Combined	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	85	152	
Units: units on a scale				
least squares mean (standard error)				
Change at: Day 3	0.7 (± 0.08)	0.7 (± 0.07)	0.8 (± 0.06)	
Change at: Day 10	1.8 (± 0.09)	2 (± 0.09)	2 (± 0.06)	

Statistical analyses

Statistical analysis title	Day 3: Ibuprofen Twice Daily vs Placebo Combined

Statistical analysis description:

Day 3: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline physician global assessment terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.354 [16]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.1

Notes:

[16] - p-value <=0.05 for treatment effects

Statistical analysis title	Day 3: Ibuprofen Thrice Daily vs Placebo Combined

Statistical analysis description:

Day 3: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined

Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.237 [17]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.07

Notes:

[17] - p-value <=0.05 for treatment effects

Statistical analysis title	Day 3: Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Day 3: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline physician global assessment terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.871 [18]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.19

Notes:

[18] - p-value <=0.05 for treatment effects

Statistical analysis title	Day 10: Ibuprofen Twice Daily vs Placebo Combined

Statistical analysis description:

Day 10: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline physician global assessment terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05 [19]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	0

Notes:

[19] - p-value <=0.05 for treatment effects

Statistical analysis title	Day 10: Ibuprofen Thrice Daily vs Placebo Combined

Statistical analysis description:

Day 10: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline physician global assessment terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.64 [20]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.25
upper limit	0.15

Notes:

[20] - p-value <=0.05 for treatment effects

Statistical analysis title	Day 10: Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Day 10: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline physician global assessment terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18 [21]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.41

Notes:

[21] - p-value <=0.05 for treatment effects

Secondary: Change From Baseline in Ankle Pain at Rest and Upon Weight Bearing (PID NRS) at Pre-specified Time Points

End point title	Change From Baseline in Ankle Pain at Rest and Upon Weight Bearing (PID NRS) at Pre-specified Time Points

End point description:

PI in ankle pain at rest and upon weight bearing was assessed on an 11-point numerical rating scale from 0=no pain to 10=most severe pain. PID was the difference between baseline PI (prior to the first dose) and current PI at assessment. Pain score at base line is usually higher than that at post baseline. So negative value of SPID indicates pain relief from baseline, while positive value means a worst pain comparing to baseline. The full analysis set included all randomized subjects who dosed with the study medication and provided a baseline assessment.

End point type	Secondary

End point timeframe:

Baseline, 1, 2, 3, 4, 5, 6, 12(Day1),24(Day2),30(Day2),36(Day2),48(Day3),50(Day3),54(Day3),60(Day3),72(Day4),78(Day4),84(Day4), 96(Day5),102(Day5), 108 (Day5),

End point values	Ibuprofen Twice Daily	Ibuprofen Thrice Daily	Placebo Combined	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	85	152	
Units: units on a scale				
least squares mean (standard error)				
Change at: At Rest 1 hour Day 1	1.3 (± 0.19)	0.7 (± 0.17)	1.2 (± 0.13)	
Change at: Upon Weight Bearing 1 hour Day 1	1.5 (± 0.2)	1.1 (± 0.18)	1.4 (± 0.14)	
Change at: At Rest 2 hour Day 1	1.7 (± 0.22)	1.2 (± 0.2)	1.5 (± 0.15)	
Change at: Upon Weight Bearing 2 hour Day 1	1.8 (± 0.23)	1.5 (± 0.21)	1.8 (± 0.16)	
Change at: At Rest 3 hour Day 1	1.9 (± 0.23)	1.2 (± 0.22)	1.6 (± 0.16)	
Change at: Upon Weight Bearing 3 hour Day 1	2.2 (± 0.25)	1.7 (± 0.23)	1.9 (± 0.17)	
Change at: At Rest 4 hour Day 1	1.8 (± 0.24)	1.2 (± 0.22)	1.5 (± 0.16)	
Change at: Upon Weight Bearing 4 hour Day 1	1.9 (± 0.25)	1.8 (± 0.23)	1.7 (± 0.18)	
Change at: At Rest 5 hour Day 1	1.9 (± 0.24)	1.1 (± 0.22)	1.4 (± 0.16)	
Upon Weight Bearing: 5 hour Day 1	2.2 (± 0.26)	1.6 (± 0.24)	1.7 (± 0.18)	
Change at: At Rest 6 hour Day 1	1.9 (± 0.24)	1.1 (± 0.22)	1.2 (± 0.16)	
Change at: Upon Weight Bearing 6 hour Day 1	2.1 (± 0.25)	1.6 (± 0.23)	1.5 (± 0.17)	
Change at: At Rest Day 1(PM)	1.8 (± 0.22)	1.1 (± 0.2)	1.2 (± 0.15)	
Change at: Upon Weight Bearing Day 1(PM)	2 (± 0.24)	1.6 (± 0.22)	1.6 (± 0.17)	
Change at: At Rest Day 2(AM)	2 (± 0.22)	1.3 (± 0.2)	1.6 (± 0.15)	
Change at: Upon Weight Bearing Day 2(AM)	2 (± 0.24)	1.8 (± 0.22)	1.9 (± 0.17)	
Change at: At Rest Day 2 Mid-day	2.3 (± 0.23)	1.7 (± 0.21)	1.8 (± 0.16)	
Change at: Upon Weight Bearing Day 2 Mid-day	2.5 (± 0.24)	2.1 (± 0.22)	2.1 (± 0.17)	
Change at: At Rest Day 2(PM)	2.2 (± 0.23)	1.9 (± 0.21)	1.8 (± 0.16)	
Change at: Upon Weight Bearing Day 2(PM)	2.4 (± 0.24)	2.4 (± 0.22)	2.1 (± 0.17)	
Change at: At Rest Day 3(AM)	2.7 (± 0.22)	2 (± 0.21)	2.1 (± 0.16)	
Change at: Upon Weight Bearing Day 3(AM)	2.8 (± 0.25)	2.7 (± 0.23)	2.5 (± 0.17)	
Change at: At Rest Day 3(AM + 2 hours)	2.8 (± 0.24)	2.2 (± 0.22)	2.2 (± 0.16)	

Change at: Upon Weight Bearing Day 3(AM + 2 hours)	2.9 (± 0.26)	2.9 (± 0.24)	2.6 (± 0.18)	
Change at: At Rest Day 3 Mid-day	3 (± 0.23)	2.2 (± 0.22)	2.3 (± 0.16)	
Change at: Upon Weight Bearing Day 3 Mid-day	3.2 (± 0.26)	2.9 (± 0.24)	2.7 (± 0.18)	
Change at: At Rest Day 3(PM)	3 (± 0.23)	2.1 (± 0.22)	2.3 (± 0.16)	
Change at: Upon Weight Bearing Day 3(PM)	3.1 (± 0.25)	2.8 (± 0.23)	2.7 (± 0.18)	
Change at: At Rest Day 4(AM)	3.2 (± 0.23)	2.5 (± 0.21)	2.6 (± 0.16)	
Change at: Upon Weight Bearing Day 4(AM)	3.4 (± 0.25)	3.2 (± 0.23)	3 (± 0.18)	
Change at: At Rest Day 4 Mid-day	3.2 (± 0.25)	2.5 (± 0.23)	2.5 (± 0.17)	
Change at: Upon Weight Bearing Day 4 Mid-day	3.5 (± 0.27)	3.3 (± 0.25)	3.2 (± 0.19)	
Change at: At Rest Day 4(PM)	3.2 (± 0.24)	2.7 (± 0.22)	2.5 (± 0.17)	
Change at: Upon Weight Bearing Day 4(PM)	3.4 (± 0.27)	3.4 (± 0.25)	3.1 (± 0.19)	
Change at: At Rest Day 5(AM)	3.3 (± 0.24)	2.8 (± 0.22)	2.7 (± 0.17)	
Change at: Upon Weight Bearing Day 5(AM)	3.7 (± 0.27)	3.5 (± 0.24)	3.3 (± 0.19)	
Change at: At Rest Day 5 Mid-day	3.4 (± 0.25)	2.9 (± 0.23)	2.7 (± 0.17)	
Change at: Upon Weight Bearing Day 5 Mid-day	3.7 (± 0.27)	3.7 (± 0.25)	3.3 (± 0.19)	
Change at: At Rest Day 5(PM)	3.4 (± 0.25)	3 (± 0.23)	2.8 (± 0.17)	
Change at: Upon Weight Bearing Day 5(PM)	3.8 (± 0.28)	3.7 (± 0.26)	3.5 (± 0.19)	
Change at: At Rest Day 6(AM)	3.5 (± 0.25)	3.2 (± 0.23)	3.1 (± 0.17)	
Change at: Upon Weight Bearing Day 6(AM)	3.9 (± 0.28)	4 (± 0.26)	3.8 (± 0.2)	
Change at: At Rest Day 6 Mid-day	3.5 (± 0.25)	3.3 (± 0.23)	3.1 (± 0.17)	
Change at: Upon Weight Bearing Day 6 Mid-day	3.8 (± 0.28)	4.1 (± 0.26)	3.7 (± 0.2)	
Change at: At Rest Day 6(PM)	3.6 (± 0.26)	3.3 (± 0.24)	2.9 (± 0.18)	
Change at: Upon Weight Bearing Day 6(PM)	3.9 (± 0.29)	4.2 (± 0.27)	3.7 (± 0.2)	
Change at: At Rest Day 7(AM)	3.6 (± 0.25)	3.5 (± 0.23)	3.1 (± 0.17)	
Change at: Upon Weight Bearing Day 7(AM)	4.2 (± 0.29)	4.5 (± 0.27)	3.9 (± 0.2)	
Change at: At Rest Day 7 Mid-day	4 (± 0.25)	3.6 (± 0.23)	3.2 (± 0.18)	
Change at: Upon Weight Bearing Day 7 Mid-day	4.6 (± 0.29)	4.5 (± 0.27)	4.1 (± 0.2)	
Change at: At Rest Day 7(PM)	3.9 (± 0.25)	3.7 (± 0.23)	3.4 (± 0.17)	
Change at: Upon Weight Bearing Day 7(PM)	4.5 (± 0.29)	4.7 (± 0.27)	4.2 (± 0.2)	

Statistical analyses

Statistical analysis title	At Rest/1 hour: Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

At Rest 1 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined

Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.771 [22]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	0.51

Notes:

[22] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/1 hour: Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

At Rest 1 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022 [23]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	-0.07

Notes:

[23] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/1 hour: Ibuprofen Twice vs Thrice Daily

Statistical analysis description:

At Rest 1 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032 [24]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.03
upper limit	-0.05

Notes:

[24] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/1 hour: Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing 1 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.72 [25]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	0.55

Notes:

[25] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/1 hour: Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing 1 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.194 [26]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.71
upper limit	0.15

Notes:

[26] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/1 hour: Ibuprofen Twice vs Thrice Daily

Statistical analysis description:

Upon Weight Bearing 1 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.163 [27]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.89
upper limit	0.15

Notes:

[27] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/2 hour:Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

At Rest 2 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.644 [28]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.64

Notes:

[28] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/2 hour:Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

At Rest 2 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined

Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.129 [29]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.85
upper limit	0.11

Notes:

[29] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/2 hour:Ibuprofen Twice Daily vs Thrice

Statistical analysis description:

At Rest 2 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.096 [30]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.07
upper limit	0.09

Notes:

[30] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/2 hour:Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing 2 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.905 [31]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0.57

Notes:

[31] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/2 hour:Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing 2 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.279 [32]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.77
upper limit	0.22

Notes:

[32] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/2 hour: Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Upon Weight Bearing 2 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.315 [33]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.29

Notes:

[33] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/3 hour: Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

At Rest 3 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.203 [34]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	0.91

Notes:

[34] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/3 hour: Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

At Rest 3 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.207 [35]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.83
upper limit	0.18

Notes:

[35] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/3 hour: Ibuprofen Twice Daily vs Thrice

Statistical analysis description:

At Rest 3 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03 [36]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	-0.07

Notes:

[36] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/3 hour: Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing 3 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.372 [37]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.84

Notes:

[37] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/3 hour: Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing 3 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.532 [38]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.36

Notes:

[38] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/3 hour: Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Upon Weight Bearing 3 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.189 [39]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.08
upper limit	0.21

Notes:

[39] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/4 hour: Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

At Rest 4 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.264 [40]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	0.87

Notes:

[40] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/4 hour: Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

At Rest 4 hour Day 1:The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.26 [41]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.81
upper limit	0.22

Notes:

[41] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/4 hour: Ibuprofen Twice Daily vs Thrice

Statistical analysis description:

At Rest 4 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.054 [42]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.23
upper limit	0.01

Notes:

[42] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/4 hour: Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing 4 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined

Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.456 [43]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	0.81

Notes:

[43] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/4 hour: Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing 4 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.639 [44]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	0.68

Notes:

[44] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/4 hour: Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Upon Weight Bearing 4 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78 [45]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.75
upper limit	0.57

Notes:

[45] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/5 hour: Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

At Rest 5 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.071 [46]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	1.07

Notes:

[46] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/5 hour: Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

At Rest 5 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.468 [47]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.32

Notes:

[47] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/5 hour: Ibuprofen Twice Daily vs Thrice

Statistical analysis description:

At Rest 5 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.027 [48]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.33
upper limit	-0.08

Notes:

[48] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/5 hour: Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing 5 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.107 [49]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	1.09

Notes:

[49] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/5 hour: Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing 5 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined

Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.947 [50]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.57
upper limit	0.53

Notes:

[50] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/5 hour: Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Upon Weight Bearing 5 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.134 [51]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.18
upper limit	0.16

Notes:

[51] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/6 hour: Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

At Rest 6 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017 [52]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	1.23

Notes:

[52] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/6 hour: Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

At Rest 6 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.715 [53]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.41

Notes:

[53] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/6 hour: Ibuprofen Twice Daily vs Thrice

Statistical analysis description:

At Rest 6 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015 [54]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.39
upper limit	-0.15

Notes:

[54] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/6 hour: Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing 6 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.027 [55]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	1.23

Notes:

[55] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/6 hour: Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing 6 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66 [56]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	0.65

Notes:

[56] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/6 hour: Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Upon Weight Bearing 6 hour Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.107 [57]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.18
upper limit	0.11

Notes:

[57] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/1(PM): Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

At Rest Day 1(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02 [58]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	1.13

Notes:

[58] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/1(PM): Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

At Rest Day 1(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.749 [59]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.55
upper limit	0.4

Notes:

[59] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/1(PM): Ibuprofen Twice Daily vs Thrice

Statistical analysis description:

At Rest Day 1(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019 [60]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.27
upper limit	-0.12

Notes:

[60] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/1(PM): Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 1(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.163 [61]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.96

Notes:

[61] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/1(PM): Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 1(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.727 [62]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	0.61

Notes:

[62] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/1(PM): Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Upon Weight Bearing Day 1(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.336 [63]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.94
upper limit	0.32

Notes:

[63] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 2(AM):Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

At Rest Day 2(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined

Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.174 [64]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.87

Notes:

[64] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day2(AM):Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

At Rest Day 2(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.277 [65]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.73
upper limit	0.21

Notes:

[65] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 2(AM):Ibuprofen Twice Daily vs Thrice

Statistical analysis description:

At Rest Day 2(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035 [66]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.19
upper limit	-0.04

Notes:

[66] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 2(AM): Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 2(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.858 [67]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0.6

Notes:

[67] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 2(AM): Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 2(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.724 [68]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.42

Notes:

[68] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 2(AM):Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Upon Weight Bearing Day 2(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.651 [69]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	0.48

Notes:

[69] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 2(MD):Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

At Rest Day 2 Mid-day(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.059 [70]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	1.05

Notes:

[70] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 2(MD):Ibuprofen Thrice DailyvsPlacebo

Statistical analysis description:

At Rest Day 2(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined

Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.766 [71]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.57
upper limit	0.42

Notes:

[71] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 2(MD):Ibuprofen Twice Daily vs Thrice

Statistical analysis description:

At Rest Day 2(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.053 [72]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.19
upper limit	0.01

Notes:

[72] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 2(MD): Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 2(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.212 [73]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	0.92

Notes:

[73] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 2(MD): Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 2(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.911 [74]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.49
upper limit	0.55

Notes:

[74] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 2(MD):Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Upon Weight Bearing Day 2(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.305 [75]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.96
upper limit	0.3

Notes:

[75] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 2(PM):Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

At Rest Day 2(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.075 [76]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	1.02

Notes:

[76] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day2(PM):Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

At Rest Day 2(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.684 [77]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.39
upper limit	0.6

Notes:

[77] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 2(PM):Ibuprofen Twice Daily vs Thrice

Statistical analysis description:

At Rest Day 2(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.208 [78]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.98
upper limit	0.21

Notes:

[78] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 2(PM): Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 2(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.304 [79]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.85

Notes:

[79] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 2(PM):Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 2(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.356 [80]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.76

Notes:

[80] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 2(PM):Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Upon Weight Bearing Day 2(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.876 [81]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.67
upper limit	0.58

Notes:

[81] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 3(AM):Ibuprofen Twice DailyvsPlacebo

Statistical analysis description:

At Rest Day 3(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02 [82]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	1.15

Notes:

[82] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 3(AM):Ibuprofen Thrice DailyvsPlacebo

Statistical analysis description:

At Rest Day 3(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.94 [83]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0.47

Notes:

[83] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 3(AM):Ibuprofen Twice Daily vs Thrice

Statistical analysis description:

At Rest Day 3(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032 [84]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.23
upper limit	-0.06

Notes:

[84] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 3(AM):Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 3(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined

Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.206 [85]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	0.95

Notes:

[85] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 3(AM):Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 3(AM):The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31 [86]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	0.81

Notes:

[86] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 3(AM):Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Upon Weight Bearing Day 3(AM):The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.771 [87]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.74
upper limit	0.55

Notes:

[87] - p-value <=0.05 for treatment effects

Statistical analysis title	Rest/Day 3(AM+2h):Ibuprofen Twice DailyvsPlacebo

Statistical analysis description:

At Rest Day 3(AM + 2 hours): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016 [88]
Method	ANOVA
Parameter estimate	LS Mean difference
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	1.24

Notes:

[88] - p-value <=0.05 for treatment effects

Statistical analysis title	Rest/Day3(AM+2h):Ibuprofen Thrice DailyvsPlacebo

Statistical analysis description:

At Rest Day 3(AM + 2 hours): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.905 [89]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	0.54

Notes:

[89] - p-value <=0.05 for treatment effects

Statistical analysis title	Rest/Day 3(AM+2h):Ibuprofen Twice Daily vs Thrice

Statistical analysis description:

At Rest Day 3(AM + 2 hours): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.039 [90]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.28
upper limit	-0.03

Notes:

[90] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 3(AM+2h):Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 3(AM + 2 hours): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.276 [91]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.93

Notes:

[91] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 3(AM+2h):Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 3(AM + 2 hours): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined

Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.343 [92]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.82

Notes:

[92] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 3(AM+2h):Ibuprofen Twice Daily vs Thrice

Statistical analysis description:

Upon Weight Bearing Day 3(AM + 2 hours): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.849 [93]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.73
upper limit	0.6

Notes:

[93] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 3(MD):Ibuprofen Twice DailyvsPlacebo

Statistical analysis description:

At Rest Day 3(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009 [94]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	1.29

Notes:

[94] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day3(MD):Ibuprofen Thrice DailyvsPlacebo

Statistical analysis description:

At Rest Day 3(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.763 [95]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	0.43

Notes:

[95] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 3(MD):Ibuprofen Twice Daily vs Thrice

Statistical analysis description:

At Rest Day 3(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01 [96]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.43
upper limit	-0.2

Notes:

[96] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 3 (MD):Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 3 (MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.105 [97]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	1.09

Notes:

[97] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 3 (MD):Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 3 (MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.533 [98]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	0.73

Notes:

[98] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 3(MD):Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Upon Weight Bearing Day 3(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.348 [99]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.99
upper limit	0.35

Notes:

[99] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 3(PM):Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

At Rest Day 3(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016 [100]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	1.23

Notes:

[100] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day3(PM):Ibuprofen Thrice DailyvsPlacebo

Statistical analysis description:

At Rest Day 3(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.483 [101]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.69
upper limit	0.33

Notes:

[101] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 3(PM):Ibuprofen Twice Daily vs Thrice

Statistical analysis description:

At Rest Day 3(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006 [102]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.47
upper limit	-0.25

Notes:

[102] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 3(PM):Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 3(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.177 [103]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	1

Notes:

[103] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 3(PM):Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 3(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.586 [104]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.7

Notes:

[104] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 3(PM):Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Upon Weight Bearing Day 3(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.448 [105]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.92
upper limit	0.41

Notes:

[105] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 4(AM):Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

At Rest Day 4(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined

Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.043 [106]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	1.09

Notes:

[106] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day4(AM):Ibuprofen Thrice DailyvsPlacebo

Statistical analysis description:

At Rest Day 4(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.688 [107]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	0.39

Notes:

[107] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 4(AM):Ibuprofen Twice Daily vs Thrice

Statistical analysis description:

At Rest Day 4(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032 [108]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.25
upper limit	-0.06

Notes:

[108] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 4(AM):Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 4(AM):The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.179 [109]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	0.99

Notes:

[109] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 4(AM):Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 4(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.609 [110]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.69

Notes:

[110] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 4(AM):Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Upon Weight Bearing Day 4(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.435 [111]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.92
upper limit	0.4

Notes:

[111] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 4(MD):Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

At Rest Day 4(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.023 [112]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	1.26

Notes:

[112] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day4(MD):Ibuprofen Thrice DailyvsPlacebo

Statistical analysis description:

At Rest Day 4(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined

Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.987 [113]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	0.53

Notes:

[113] - p-value <=0.05 for treatment effects

Statistical analysis title	AtRest/Day4(MD):IbuprofenTwice DailyvsThrice Daily

Statistical analysis description:

At Rest Day 4(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04 [114]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.33
upper limit	-0.03

Notes:

[114] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 4(MD):Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 4(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.319 [115]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	0.94

Notes:

[115] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 4(MD):Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 4(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.712 [116]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	0.69

Notes:

[116] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 4(PM):Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Upon Weight Bearing Day 4(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.557 [117]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.91
upper limit	0.49

Notes:

[117] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day4(PM): Ibuprofen Twice DailyvsPlacebo

Statistical analysis description:

At Rest Day 4(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015 [118]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	1.28

Notes:

[118] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day4(PM): Ibuprofen Twice DailyvsPlacebo

Statistical analysis description:

At Rest Day 4(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.326 [119]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	0.79

Notes:

[119] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 4(PM): Ibuprofen Twice Daily vs Thrice

Statistical analysis description:

At Rest Day 4(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.167 [120]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.08
upper limit	0.19

Notes:

[120] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 4(PM): Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 4(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.35 [121]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	0.93

Notes:

[121] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 4(PM):Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 4(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.235 [122]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.93

Notes:

[122] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 4(PM):Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Upon Weight Bearing Day 4(PM):The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.881 [123]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.65
upper limit	0.76

Notes:

[123] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day5(AM): Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

At Rest Day 5(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.036 [124]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	1.16

Notes:

[124] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day5(AM):Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

At Rest Day 5(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.656 [125]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.63

Notes:

[125] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 5(AM):Ibuprofen Twice Daily vs Thrice

Statistical analysis description:

At Rest Day 5(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13 [126]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.11
upper limit	0.14

Notes:

[126] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 5(AM):Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 5(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined

Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.304 [127]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.95

Notes:

[127] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 5(AM):Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 5(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.491 [128]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	0.78

Notes:

[128] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 5(AM):Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Upon Weight Bearing Day 5(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.726 [129]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.82
upper limit	0.57

Notes:

[129] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 5(MD):Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

At Rest Day 5(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.029 [130]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	1.23

Notes:

[130] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day5(MD):Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

At Rest Day 5(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.585 [131]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.39
upper limit	0.68

Notes:

[131] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 5(MD):Ibuprofen Twice Daily vs Thrice

Statistical analysis description:

At Rest Day 5(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.131 [132]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.15
upper limit	0.15

Notes:

[132] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 5(MD):Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 5(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.215 [133]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	1.04

Notes:

[133] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 5(MD):Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 5(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined

Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.244 [134]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	0.94

Notes:

[134] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 5(PM):Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

At Rest Day 5(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.067 [135]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	1.13

Notes:

[135] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 5(MD):Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Upon Weight Bearing Day 5(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.885 [136]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	0.66

Notes:

[136] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day5(PM):Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

At Rest Day 5(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5 [137]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	0.73

Notes:

[137] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 5(PM):Ibuprofen Twice Daily vs Thrice

Statistical analysis description:

At Rest Day 5(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.276 [138]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.02
upper limit	0.29

Notes:

[138] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 5(PM):Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 5(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.413 [139]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	0.92

Notes:

[139] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 5(PM):Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 5(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.448 [140]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	0.83

Notes:

[140] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 5(PM):Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Upon Weight Bearing Day 5(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.917 [141]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	0.69

Notes:

[141] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 6(AM):Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

At Rest Day 6(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.132 [142]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	1.03

Notes:

[142] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day6(AM):Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

At Rest Day 6(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.505 [143]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	0.72

Notes:

[143] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 6(AM):Ibuprofen Twice Daily vs Thrice

Statistical analysis description:

At Rest Day 6(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.422 [144]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.92
upper limit	0.38

Notes:

[144] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 6(AM):Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 6(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.386 [145]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	0.87

Notes:

[145] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 6(AM):Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 6(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.747 [146]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	0.76

Notes:

[146] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 6(AM):Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Upon Weight Bearing Day 6(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.668 [147]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.57
upper limit	0.89

Notes:

[147] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 6(MD):Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

At Rest Day 6(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined

Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.099 [148]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	1.08

Notes:

[148] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day6(MD):Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

At Rest Day 6(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.365 [149]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.79

Notes:

[149] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 6(MD):Ibuprofen Twice Daily vs Thrice

Statistical analysis description:

At Rest Day 6(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.463 [150]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.41

Notes:

[150] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 6(MD):Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 6(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.845 [151]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.73

Notes:

[151] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 6(MD):Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 6(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.199 [152]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	1.02

Notes:

[152] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 6(MD):Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Upon Weight Bearing Day 6(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.375 [153]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	1.08

Notes:

[153] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 6(PM):Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

At Rest Day 6(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.028 [154]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	1.27

Notes:

[154] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day6(PM):Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

At Rest Day 6(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined

Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.188 [155]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.92

Notes:

[155] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 6(PM):Ibuprofen Twice Daily vs Thrice

Statistical analysis description:

At Rest Day 6(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.375 [156]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.97
upper limit	0.37

Notes:

[156] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 6(PM):Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 6(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.552 [157]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	0.89

Notes:

[157] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 6(PM):Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 6(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.126 [158]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	1.12

Notes:

[158] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 6(PM):Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Upon Weight Bearing Day 6(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.46 [159]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	1.05

Notes:

[159] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 7(AM):Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

At Rest Day 7(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.095 [160]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	1.09

Notes:

[160] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day7(AM):Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

At Rest Day 7(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.146 [161]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.94

Notes:

[161] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 7(AM):Ibuprofen Twice Daily vs Thrice

Statistical analysis description:

At Rest Day 7(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.769 [162]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.75
upper limit	0.56

Notes:

[162] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 7(AM):Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 7(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.405 [163]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.39
upper limit	0.96

Notes:

[163] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 7(AM):Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 7(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.073 [164]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	1.2

Notes:

[164] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 7(AM):Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Upon Weight Bearing Day 7(AM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.458 [165]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	1.04

Notes:

[165] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 7(MD):Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

At Rest Day 7(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009 [166]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	1.39

Notes:

[166] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day7(MD):Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

At Rest Day 7(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.209 [167]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.9

Notes:

[167] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 7(MD):Ibuprofen Twice Daily vs Thrice

Statistical analysis description:

At Rest Day 7(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.193 [168]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.11
upper limit	0.22

Notes:

[168] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 7(MD):Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 7(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined

Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.149 [169]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	1.18

Notes:

[169] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 7(MD):Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 7(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.186 [170]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	1.06

Notes:

[170] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 7(MD):Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Upon Weight Bearing Day 7(MD): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.845 [171]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.84
upper limit	0.69

Notes:

[171] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day7(PM): Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

At Rest Day 7(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.067 [172]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	1.14

Notes:

[172] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day7(PM): Ibuprofen Thrice Dailyvs Placebo

Statistical analysis description:

At Rest Day 7(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.242 [173]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	0.87

Notes:

[173] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest/Day 7(PM): Ibuprofen Twice Daily vs Thrice

Statistical analysis description:

At Rest Day 7(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.498 [174]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	0.43

Notes:

[174] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 7(PM): Ibuprofen Twice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 7(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33 [175]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	1.02

Notes:

[175] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 7(PM): Ibuprofen Thrice Daily vs Placebo

Statistical analysis description:

Upon Weight Bearing Day 7(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined

Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.124 [176]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	1.13

Notes:

[176] - p-value <=0.05 for treatment effects

Statistical analysis title	WB/Day 7(PM):Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Upon Weight Bearing Day 7(PM): The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.687 [177]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.61
upper limit	0.92

Notes:

[177] - p-value <=0.05 for treatment effects

Secondary: Sum of Pain Intensity Difference at Rest and on Weight Bearing Over 6 Hours on Day 1 and Over 2 Hours on Day 3

End point title	Sum of Pain Intensity Difference at Rest and on Weight Bearing Over 6 Hours on Day 1 and Over 2 Hours on Day 3

End point description:

PI at rest and on weight bearing was assessed on an 11-point numerical rating scale from 0=no pain to 10=most severe pain. PID was the difference between baseline PI (prior to the first dose) and current PI at assessment. SPID 0-6 was calculated as the time-weighted sum of PID scores over 6 hours on Day 1, with a total score ranges from -30 (worst) to 36 (best). SPID 0-12 was calculated as the time weighted sum of PID scores over 2 hours on Day 3, with a total score ranges from -10 (worst) to 12 (best). SPID is a value of change from baseline. Pain score at base line is usually higher than that at post baseline. So negative value of SPID indicates pain relief from baseline, while positive value means a worst pain comparing to baseline, a negative value of SPID indicates higher pain relief from baseline. The full analysis set included all randomized subjects who dosed with the study medication and provided a baseline assessment.

End point type	Secondary

End point timeframe:

Over 6 hours on Day 1, over 2 hours on Day 3

End point values	Ibuprofen Twice Daily	Ibuprofen Thrice Daily	Placebo Combined	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	85	152	
Units: units on a scale				
least squares mean (standard error)				
At Rest over 6 Hours on Day 1	10.4 (± 1.24)	6.6 (± 1.14)	8.4 (± 0.86)	
Weight Bearing over 6 Hours on Day 1	11.7 (± 1.31)	9.4 (± 1.2)	9.9 (± 0.91)	
At Rest over 2 Hours on Day 3	109.6 (± 9.54)	79.4 (± 8.8)	84.7 (± 6.6)	
Weight Bearing over 2 Hours on Day 3	116.1 (± 10.11)	106.8 (± 9.29)	102.4 (± 7.06)	

Statistical analyses

Statistical analysis title	At Rest over 6 Hours on Day 1

Statistical analysis description:

At Rest over 6 Hours on Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.166 [178]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.85
upper limit	4.95

Notes:

[178] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest over 6 Hours on Day 1

Statistical analysis description:

At Rest over 6 Hours on Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined

Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.199 [179]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.42
upper limit	0.93

Notes:

[179] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest over 6 Hours on Day 1

Statistical analysis description:

At Rest over 6 Hours on Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022 [180]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-3.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.04
upper limit	-0.56

Notes:

[180] - p-value <=0.05 for treatment effects

Statistical analysis title	Weight Bearing over 6 Hours on Day 1

Statistical analysis description:

Weight Bearing over 6 Hours on Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.26 [181]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	1.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	4.79

Notes:

[181] - p-value <=0.05 for treatment effects

Statistical analysis title	Weight Bearing over 6 Hours on Day 1

Statistical analysis description:

Weight Bearing over 6 Hours on Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.729 [182]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.31
upper limit	2.32

Notes:

[182] - p-value <=0.05 for treatment effects

Statistical analysis title	Weight Bearing over 6 Hours on Day 1

Statistical analysis description:

Weight Bearing over 6 Hours on Day 1: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.196 [183]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.64
upper limit	1.16

Notes:

[183] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest over 2 Hours on Day 3

Statistical analysis description:

At Rest over 2 Hours on Day 3: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03 [184]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	24.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.49
upper limit	47.28

Notes:

[184] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest over 2 Hours on Day 3

Statistical analysis description:

At Rest over 2 Hours on Day 3: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.018 [185]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-30.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-55.24
upper limit	-5.23

Notes:

[185] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest over 2 Hours on Day 3

Statistical analysis description:

At Rest over 2 Hours on Day 3: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.611 [186]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-5.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.98
upper limit	15.29

Notes:

[186] - p-value <=0.05 for treatment effects

Statistical analysis title	Weight Bearing over 2 Hours on Day 3

Statistical analysis description:

Weight Bearing over 2 Hours on Day 3: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.251 [187]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	13.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.8
upper limit	37.36

Notes:

[187] - p-value <=0.05 for treatment effects

Statistical analysis title	Weight Bearing over 2 Hours on Day 3

Statistical analysis description:

Weight Bearing over 2 Hours on Day 3: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.689 [188]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	4.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.37
upper limit	26.26

Notes:

[188] - p-value <=0.05 for treatment effects

Statistical analysis title	Weight Bearing over 2 Hours on Day 3

Statistical analysis description:

Weight Bearing over 2 Hours on Day 3: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.486 [189]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-9.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.69
upper limit	17.01

Notes:

[189] - p-value <=0.05 for treatment effects

Secondary: Sum of Pain Intensity Difference Scores at Rest Over 3 Days

End point title	Sum of Pain Intensity Difference Scores at Rest Over 3 Days

End point description:

PI was assessed on an 11-point numerical rating scale from 0=no pain to 10=most severe pain. PID was the difference between baseline PI (prior to the first dose) and current PI at assessment. SPID was calculated as the time-weighted sum of PID scores over 3 days (72 hours). Total score ranges from -360 (worst) to 432 (best). SPID is a value of change from baseline. Pain score at base line is usually higher than that at post baseline. So negative value of SPID indicates pain relief from baseline, while positive value means a worst pain comparing to baseline, a negative value of SPID indicates higher pain relief from baseline. The full analysis set included all randomized subjects who dosed with the study medication and provided a baseline assessment.

End point type	Secondary

End point timeframe:

Over 3 Days (0-72 hours)

End point values	Ibuprofen Twice Daily	Ibuprofen Thrice Daily	Placebo Combined	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	85	152	
Units: Units on a scale				
least squares mean (standard error)	177.6 (± 13.9)	131.1 (± 12.83)	139 (± 9.62)	

Statistical analyses

Statistical analysis title	Over3Days:Ibuprofen Twice DailyvsPlacebo Combined

Statistical analysis description:

At Rest Over 3 Days: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.021 [190]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	38.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.9
upper limit	71.18

Notes:

[190] - p-value <=0.05 for treatment effects

Statistical analysis title	Over3Days:Ibuprofen Thrice DailyvsPlacebo Combined

Statistical analysis description:

At Rest Over 3 Days: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.603 [191]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-7.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.02
upper limit	22.12

Notes:

[191] - p-value <=0.05 for treatment effects

Statistical analysis title	Over 3 Days: Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

At Rest Over 3 Days: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013 [192]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-46.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-82.93
upper limit	-10.05

Notes:

[192] - p-value <=0.05 for treatment effects

Secondary: Sum of Pain Intensity Difference Scores at Rest and on Weight Bearing Over 7 Days

End point title	Sum of Pain Intensity Difference Scores at Rest and on Weight Bearing Over 7 Days

End point description:

PI was assessed on an 11-point numerical rating scale from 0=no pain to 10=most severe pain. PID was the difference between baseline PI (prior to the first dose) and current PI at assessment. SPID was calculated as the time-weighted sum of PID scores over 7 days (168 hours). Total score ranges from -840 (higher pain relief) to 1008 (lower pain relief). SPID is a value of change from baseline. Pain score at base line is usually higher than that at post baseline. So negative value of SPID indicates pain relief from baseline, while positive value means a worst pain comparing to baseline, a negative value of SPID indicates higher pain relief from baseline. The full analysis set included all randomized subjects who dosed with the study medication and provided a baseline assessment.

End point type	Secondary

End point timeframe:

Over 7 days (0-168 hours)

End point values	Ibuprofen Twice Daily	Ibuprofen Thrice Daily	Placebo Combined	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	85	152	
Units: Units on a scale				
least squares mean (standard error)				
At Rest: Over 7 Days	472.5 (± 31.6)	396.6 (± 29.16)	384.8 (± 21.88)	
Weight Bearing: Over 7 Days	516.4 (± 34.52)	507.7 (± 31.7)	470.4 (± 24.09)	

Statistical analyses

Statistical analysis title	At Rest: Ibuprofen Twice Daily vs Placebo Combined

Statistical analysis description:

At Rest Over 7 days: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.021 [193]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	87.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.48
upper limit	161.85

Notes:

[193] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest:Ibuprofen Thrice Daily vs Placebo Combined

Statistical analysis description:

At Rest Over 7 days: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.735 [194]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	11.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-56.59
upper limit	80.11

Notes:

[194] - p-value <=0.05 for treatment effects

Statistical analysis title	At Rest: Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

At Rest Over 7 days: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity at rest terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.072 [195]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-75.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-158.73
upper limit	6.93

Notes:

[195] - p-value <=0.05 for treatment effects

Statistical analysis title	WB: Ibuprofen Twice Daily vs Placebo Combined

Statistical analysis description:

Weight Bearing Over 7 Days: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.261 [196]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.43
upper limit	126.52

Notes:

[196] - p-value <=0.05 for treatment effects

Statistical analysis title	WB: Ibuprofen Thrice Daily vs Placebo Combined

Statistical analysis description:

Weight Bearing Over 7 Days: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.325 [197]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	37.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.13
upper limit	111.8

Notes:

[197] - p-value <=0.05 for treatment effects

Statistical analysis title	WB: Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Weight Bearing Over 7 Days: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline pain intensity on weight bearing terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.849 [198]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-8.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-98.64
upper limit	81.22

Notes:

[198] - p-value <=0.05 for treatment effects

Secondary: Change From Baseline in Subject Assessment of Normal Function and Activity at Day 3 and 10

End point title	Change From Baseline in Subject Assessment of Normal Function and Activity at Day 3 and 10

End point description:

Subject assessment of normal function was measured using a 5-point scale: 1= Normal walking/activity and no pain; 2= Normal walking/activity with pain; 3= Mildly restricted walking due to pain and can't resume normal activities; 4= Moderately restricted walking due to pain and can't resume normal activities; 5= Severely restricted walking due to pain and can't resume normal activities. The normal functioning and activity scores for each question range from 1 to 5, with higher scores indicating worsening of normal activity. The full analysis set included all randomized subjects who dosed with the study medication and provided a baseline assessment.

End point type	Secondary

End point timeframe:

Baseline, Day 3, 10

End point values	Ibuprofen Twice Daily	Ibuprofen Thrice Daily	Placebo Combined	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	85	152	
Units: Units on a scale				
least squares mean (standard error)				
Change at: Day 3	1 (± 0.1)	0.9 (± 0.09)	0.7 (± 0.07)	
Change at: Day 10	2.1 (± 0.07)	2.1 (± 0.09)	2.1 (± 0.09)	

Statistical analyses

Statistical analysis title	Day 3: Ibuprofen Twice Daily vs Placebo Combined

Statistical analysis description:

Day 3: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline subject assessment of Normal Function/Activity terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.042 [199]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.49

Notes:

[199] - p-value <=0.05 for treatment effects

Statistical analysis title	Day 3: Ibuprofen Thrice Daily vs Placebo Combined

Statistical analysis description:

Day 3: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline subject assessment of Normal Function/Activity terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.114 [200]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.4

Notes:

[200] - p-value <=0.05 for treatment effects

Statistical analysis title	Day 3: Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Day 3: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline subject assessment of Normal Function/Activity terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.598 [201]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	0.2

Notes:

[201] - p-value <=0.05 for treatment effects

Statistical analysis title	Day 10: Ibuprofen Twice Daily vs Placebo Combined

Statistical analysis description:

Day 10: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline subject assessment of Normal Function/Activity terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.833 [202]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	0.19

Notes:

[202] - p-value <=0.05 for treatment effects

Statistical analysis title	Day 10: Ibuprofen Thrice Daily vs Placebo Combined

Statistical analysis description:

Day 10: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline subject assessment of Normal Function/Activity terms. Upper limit of 95% CI < 0 for Ibuprofen treatment significantly better than combined Placebo.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined

Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.853 [203]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.22

Notes:

[203] - p-value <=0.05 for treatment effects

Statistical analysis title	Day 10: Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Day 10: The ANOVA model was used which contains treatment, baseline categorical pain severity rating, pooled site block, and baseline subject assessment of Normal Function/Activity terms.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.733 [204]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.29

Notes:

[204] - p-value <=0.05 for treatment effects

Secondary: Subject’s Global Assessment of Medication at End of Study

End point title	Subject’s Global Assessment of Medication at End of Study

End point description:

Subjects Global Assessment of Medication was used to rate the medication as a pain reliever. The responses of subjects were recorded using five-point scale: 1= Very Poor, 2= Poor, 3= Fair, 4= Good, 5= Very Good. The global assessment of medication scores for each question range from 0 to 5, giving a possible score range of 0 - 5, with higher scores indicating medication as a better pain reliever. The full analysis set included all randomized subjects who dosed with the study medication and provided a baseline assessment. Number of subjects analyzed 'N' signifies those subjects who were evaluable for the measure.

End point type	Secondary

End point timeframe:

Day 10

End point values	Ibuprofen Twice Daily	Ibuprofen Thrice Daily	Placebo Combined	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	75	141	
Units: Units on a scale				
arithmetic mean (standard deviation)	3.8 (± 1.18)	4 (± 0.94)	4 (± 1.03)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Perceptible Relief and Meaningful Relief

End point title	Time to First Perceptible Relief and Meaningful Relief

End point description:

Subjects evaluated time to first perceptible relief by stopping stopwatch labelled 'first perceptible relief' at moment subject first began to experience any relief, exact question:"Stop stopwatch when you first begin to feel any pain-relieving effect whatsoever of product".First perceptible relief considered confirmed by meaningful relief if subject achieved both"first perceptible","meaningful" relief by either pressing second stopwatch or by indicating that his "first perceptible" relief was also"meaningful".For"time to meaningful relief," exact question asked:"Stop stopwatch when you have meaningful relief."Stopwatches were active up to 3 hours after dosing or until stopped by subject, or rescue medication was administered.The full analysis set included all randomized subjects who dosed with the study medication and provided a baseline assessment."99999" in the median and confidence interval values signifies not estimable, since median was greater than 180 min.

End point type	Secondary

End point timeframe:

0 to 3 hours on Day 1

End point values	Ibuprofen Twice Daily	Ibuprofen Thrice Daily	Placebo Combined	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	85	152	
Units: Minutes				
median (confidence interval 95%)				
First Perceptible Relief	12.9 (10.1 to 15.7)	36.4 (24.7 to 56.4)	22.7 (15.7 to 30.3)	
Meaningful Relief	41.6 (31.6 to 67.5)	99999 (99999 to 99999)	72.6 (58.1 to 116.1)	

Statistical analyses

Statistical analysis title	FPF: Ibuprofen Twice Daily vs Placebo Combined

Statistical analysis description:

Time to First Perceptible Relief (FPF): Hazard Ratio and corresponding 95% CI were calculated based on the Wald statistic from the Proportional Hazards (PH) model with treatment, BLPSR, and pooled site blocks.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined

Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016 [205]
Method	Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.07
upper limit	1.97

Notes:

[205] - p-value <=0.05 for treatment effects

Statistical analysis title	FPF: Ibuprofen Thrice Daily vs Placebo Combined

Statistical analysis description:

Time to FPF: Hazard Ratio and corresponding 95% CI were calculated based on the Wald statistic from the PH model with treatment, BLPSR, and pooled site blocks.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022 [206]
Method	Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	0.95

Notes:

[206] - p-value <=0.05 for treatment effects

Statistical analysis title	FPF: Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Time to FPF: Hazard Ratio and corresponding 95% CI were calculated based on the Wald statistic from the PH model with treatment, BLPSR, and pooled site blocks.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [207]
Method	Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.49

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	0.69

Notes:

[207] - p-value <=0.05 for treatment effects

Statistical analysis title	MR: Ibuprofen Twice Daily vs Placebo Combined

Statistical analysis description:

Time to Meaningful Relief (MR): Hazard Ratio and corresponding 95% CI were calculated based on the Wald statistic from the PH model with treatment, BLPSR, and pooled site blocks.

Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [208]
Method	Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.27
upper limit	2.51

Notes:

[208] - p-value <=0.05 for treatment effects

Statistical analysis title	MR: Ibuprofen Thrice Daily vs Placebo Combined

Statistical analysis description:

Time to MR: Hazard Ratio and corresponding 95% CI were calculated based on the Wald statistic from the PH model with treatment, BLPSR, and pooled site blocks.

Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009 [209]
Method	Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	0.88

Notes:

[209] - p-value <=0.05 for treatment effects

Statistical analysis title	MR: Ibuprofen Twice Daily vs Thrice Daily

Statistical analysis description:

Time to MR: Hazard Ratio and corresponding 95% CI were calculated based on the Wald statistic from the PH model with treatment, BLPSR, and pooled site blocks.

Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [210]
Method	Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	0.52

Notes:

[210] - p-value <=0.05 for treatment effects

Secondary: Time to Rescue Medication After Initial Dose, and After Each Subsequent Dose

End point title	Time to Rescue Medication After Initial Dose, and After Each Subsequent Dose

End point description:

Subjects used only acetaminophen at a dose of 500 milligram (mg) every 6 hours product as needed (PRN) as rescue medication during the course of the study. Subjects who used acetaminophen were to record its use, and date and time of administration in the subject diary. Time to rescue medication after initial dose, after each subsequent dose, provided that in each dose interval at least 25% of the subjects take rescue medication was analyzed using the proportional hazard model with site, treatment group, and baseline categorical ankle pain terms in the model. Data was not analyzed since <20% subjects used rescue medication.

End point type	Secondary

End point timeframe:

Post-Dose on Day 1 up to Day 10

End point values	Ibuprofen Twice Daily	Ibuprofen Thrice Daily	Placebo Combined	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[211]	0[212]	0[213]	
Units: Minutes				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[211] - Data was not analyzed since <20% subjects used rescue medication.

[212] - Data was not analyzed since <20% subjects used rescue medication.

[213] - Data was not analyzed since <20% subjects used rescue medication.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Doses of Rescue Medication Used During the First 7 Days of

Dosing	
End point title	Number of Doses of Rescue Medication Used During the First 7 Days of Dosing

End point description:

Subjects received only acetaminophen 500 mg every 6 hours PRN as rescue medication during the course of the study. The full analysis set included all randomized subjects who dosed with the study medication and provided a baseline assessment.

End point type	Secondary

End point timeframe:

Baseline up to Day 7

End point values	Ibuprofen Twice Daily	Ibuprofen Thrice Daily	Placebo Combined	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	85	152	
Units: Doses				
arithmetic mean (standard deviation)	1.7 (± 3.83)	0.6 (± 1.41)	1.2 (± 3.96)	

Statistical analyses

Statistical analysis title	Ibuprofen Twice Daily vs Placebo Combined
Comparison groups	Ibuprofen Twice Daily v Placebo Combined
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.479 [214]
Method	Cochran-Mantel-Haenszel

Notes:

[214] - p-values from the Cochran-Mantel-Haenszel (CMH) test with modified ridit scores, controlling for BLPSR and site block.

Statistical analysis title	Ibuprofen Thrice Daily vs Placebo Combined
Comparison groups	Ibuprofen Thrice Daily v Placebo Combined
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.279 [215]
Method	Cochran-Mantel-Haenszel

Notes:

[215] - p-values from the CMH test with modified ridit scores, controlling for BLPSR and site block.

Statistical analysis title	Ibuprofen Twice Daily vs Thrice Daily
Comparison groups	Ibuprofen Twice Daily v Ibuprofen Thrice Daily

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.129 [216]
Method	Cochran-Mantel-Haenszel

Notes:

[216] - p-values from the CMH test with modified ridit scores, controlling for BLPSR and site block.

Secondary: Percentage of Subjects Taking Rescue Medication

End point title	Percentage of Subjects Taking Rescue Medication

End point description:

Subjects used only acetaminophen at a dose of 500 mg every 6 hours PRN as analgesia or rescue therapy during the course of the study. Subjects who used acetaminophen were to record its use, and date and time of administration in the subject diary. The full analysis set included all randomized subjects who dosed with the study medication and provided a baseline assessment.

End point type	Secondary

End point timeframe:

Post first dose Day 1 up to Day 10

End point values	Ibuprofen Twice Daily	Ibuprofen Thrice Daily	Placebo Combined	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	67	85	152	
Units: Percentage of subjects				
number (not applicable)	28.4	18.8	25.7	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to 14 days after last study drug dose administration	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Ibuprofen Thrice Daily
Reporting group description:	
Ibuprofen 5% Topical Gel thrice a day was applied topically as a 4-inch strip approximately every 6 hours, for the first 7 days. Subsequently, on Days 8 through 10, subjects were permitted to use the study medication on an optional basis, according to the assigned dosing regimen.	
Reporting group title	Ibuprofen Twice Daily
Reporting group description:	
Ibuprofen 5 percent (%) topical gel twice daily was applied topically as a 4-inch strip approximately every 12 hours, for the first 7 days. Subsequently, on Days 8 through 10, subjects were permitted to use the study medication on an optional basis, according to the assigned dosing regimen.	
Reporting group title	Placebo Combined
Reporting group description:	
Placebo matched to Ibuprofen twice daily or thrice daily regimen was applied for first 7 days.	

Serious adverse events	Ibuprofen Thrice Daily	Ibuprofen Twice Daily	Placebo Combined
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 85 (0.00%)	0 / 67 (0.00%)	0 / 152 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

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

Non-serious adverse events	Ibuprofen Thrice Daily	Ibuprofen Twice Daily	Placebo Combined
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 85 (5.88%)	4 / 67 (5.97%)	13 / 152 (8.55%)
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 85 (1.18%)	0 / 67 (0.00%)	0 / 152 (0.00%)
occurrences (all)	1	0	0
Contusion			

subjects affected / exposed	0 / 85 (0.00%)	0 / 67 (0.00%)	1 / 152 (0.66%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 85 (1.18%)	0 / 67 (0.00%)	4 / 152 (2.63%)
occurrences (all)	1	0	4
Dizziness			
subjects affected / exposed	0 / 85 (0.00%)	1 / 67 (1.49%)	0 / 152 (0.00%)
occurrences (all)	0	1	0
Hypoaesthesia			
subjects affected / exposed	0 / 85 (0.00%)	0 / 67 (0.00%)	1 / 152 (0.66%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 85 (0.00%)	1 / 67 (1.49%)	1 / 152 (0.66%)
occurrences (all)	0	1	1
Application site erythema			
subjects affected / exposed	0 / 85 (0.00%)	0 / 67 (0.00%)	1 / 152 (0.66%)
occurrences (all)	0	0	1
Influenza like illness			
subjects affected / exposed	0 / 85 (0.00%)	1 / 67 (1.49%)	0 / 152 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Eye irritation			
subjects affected / exposed	0 / 85 (0.00%)	0 / 67 (0.00%)	1 / 152 (0.66%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 85 (0.00%)	0 / 67 (0.00%)	1 / 152 (0.66%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	0 / 85 (0.00%)	0 / 67 (0.00%)	1 / 152 (0.66%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	1 / 85 (1.18%)	0 / 67 (0.00%)	0 / 152 (0.00%)
occurrences (all)	1	0	0

Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	2 / 85 (2.35%)	1 / 67 (1.49%)	0 / 152 (0.00%)
occurrences (all)	2	1	0
Pruritus			
subjects affected / exposed	0 / 85 (0.00%)	0 / 67 (0.00%)	1 / 152 (0.66%)
occurrences (all)	0	0	1
Sticky skin			
subjects affected / exposed	0 / 85 (0.00%)	0 / 67 (0.00%)	1 / 152 (0.66%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 85 (0.00%)	0 / 67 (0.00%)	1 / 152 (0.66%)
occurrences (all)	0	0	1
Metatarsalgia			
subjects affected / exposed	0 / 85 (0.00%)	0 / 67 (0.00%)	1 / 152 (0.66%)
occurrences (all)	0	0	1
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 85 (0.00%)	0 / 67 (0.00%)	1 / 152 (0.66%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported