



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 | - | | |
|--------------------|---|--|--|

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| |
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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 (\pm 5.03) | 41.1 (\pm 4.62) | 42.1 (\pm 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 (\pm 4.65) | 29.4 (\pm 4.29) | 34.7 (\pm 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: | |
| <p>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.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| <p>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),</p> | |

| 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 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 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: | |
| <p>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.</p> | |
| 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 (\pm 13.9) | 131.1 (\pm 12.83) | 139 (\pm 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 occurrences (all) | 0 / 85 (0.00%) 0 | 0 / 67 (0.00%) 0 | 1 / 152 (0.66%) 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