



Clinical trial results:

A SINGLE-DOSE, RANDOMIZED, TWO-PERIOD, Crossover STUDY TO ASSESS BIOEQUIVALENCE BETWEEN TWO IBUPROFEN 200 MG TABLET FORMULATIONS, IN HEALTHY ADULTS

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2013-001442-34 |
| Trial protocol | SE |
| Global end of trial date | 24 September 2013 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 13 July 2016 |
| First version publication date | 03 August 2015 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | IBUPAI0002 |
|-----------------------|------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | McNeil AB |
| Sponsor organisation address | Box 941, Norrbroplatsen 2, Helsingborg, Sweden, SE-251 09 |
| Public contact | Elisabeth Kruse, McNeil AB, +46 42 288555, EKruse@its.jnj.com |
| Scientific contact | Maj Ablad-Jacobson, McNeil AB, +46 42 289374, MAbladJa@its.jnj.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 | 31 January 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 24 September 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 24 September 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to show bioequivalence between Ipren film coated tablet 200 mg and Brufen film coated tablet 200 mg, with respect to the single-dose pharmacokinetics of S-(+) ibuprofen. The maximum observed plasma concentrations (C_{max}), and the areas under the concentration-vs.-time curve until last measurable concentration (AUC_t), were compared to assess bioequivalence.

Protection of trial subjects:

Ethical Conduct of the Study

This study was conducted in accordance with the final protocol and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines, including ICH E6. In addition, all local regulatory requirements and laws were followed.

Subject Information and Consent

Written informed consent was obtained before initiation of any protocol-specified activities. The investigator explained the nature, purpose, and possible risks associated with study participation to each subject. Each subject was informed that he/she could withdraw from the study at any time and for any reason. Each subject was given sufficient time to consider the implications of the study before deciding whether to participate. Subjects who chose to participate signed an informed consent document.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 26 August 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 | Sweden: 30 |
| Worldwide total number of subjects | 30 |
| EEA total number of subjects | 30 |

Notes:

Subjects enrolled per age group

| | |
|--|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| | |
|--|----|
| wk | |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 30 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of 41 subjects screened for entry into the study, 30 healthy subjects were randomized to treatment. After randomization one subject withdrew his consent. Accordingly 29 subjects completed both treatments in the study.

Period 1

| | |
|------------------------------|-------------------------------|
| Period 1 title | Treatment Period 1 (24 hours) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|----|
| Are arms mutually exclusive? | No |
|------------------------------|----|

| | |
|------------------|--------------------------------------|
| Arm title | Sequence 1: Ipren followed by Brufen |
|------------------|--------------------------------------|

Arm description:

Participants received Ipren in Treatment Period 1 and Brufen in Treatment Period 2. The washout period between the 24 hours treatment periods was at least 48 hours.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ipren |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received Ipren 200 milligram (mg) tablet orally once daily on day 1 of each treatment period.

| | |
|--|--------------------|
| Investigational medicinal product name | Brufen |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received Brufen 200 milligram (mg) tablet orally once daily on day 1 of each treatment period.

| | |
|------------------|--------------------------------------|
| Arm title | Sequence 2: Brufen followed by Ipren |
|------------------|--------------------------------------|

Arm description:

Participants received Brufen in Treatment Period 1 and Ipren in Treatment Period 2. The washout period between the 24 hours treatment periods was at least 48 hours.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ipren |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received Ipren 200 milligram (mg) tablet orally once daily on day 1 of each treatment period.

| | |
|--|--------------------|
| Investigational medicinal product name | Brufen |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received Brufen 200 milligram (mg) tablet orally once daily on day 1 of each treatment period.

| Number of subjects in period 1 | Sequence 1: Ipren followed by Brufen | Sequence 2: Brufen followed by Ipren |
|--------------------------------|--------------------------------------|--------------------------------------|
| Started | 15 | 15 |
| Completed | 15 | 15 |

Period 2

| | |
|------------------------------|-------------------------|
| Period 2 title | Washout (48 hours) |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--------------------------------------|
| Are arms mutually exclusive? | No |
| Arm title | Sequence 1: Ipren followed by Brufen |

Arm description:

Participants received Ipren in Treatment Period 1 and Brufen in Treatment Period 2. The washout period between the 24 hours treatment periods was at least 48 hours.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ipren |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received Ipren 200 milligram (mg) tablet orally once daily on day 1 of each treatment period.

| | |
|--|--------------------|
| Investigational medicinal product name | Brufen |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received Brufen 200 milligram (mg) tablet orally once daily on day 1 of each treatment period.

| | |
|------------------|--------------------------------------|
| Arm title | Sequence 2: Brufen followed by Ipren |
|------------------|--------------------------------------|

Arm description:

Participants received Brufen in Treatment Period 1 and Ipren in Treatment Period 2. The washout period between the 24 hours treatment periods was at least 48 hours.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ipren |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received Ipren 200 milligram (mg) tablet orally once daily on day 1 of each treatment period.

| | |
|--|--------------------|
| Investigational medicinal product name | Brufen |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received Brufen 200 milligram (mg) tablet orally once daily on day 1 of each treatment period.

| Number of subjects in period 2 | Sequence 1: Ipren followed by Brufen | Sequence 2: Brufen followed by Ipren |
|---------------------------------------|--------------------------------------|--------------------------------------|
| Started | 15 | 15 |
| Completed | 15 | 14 |
| Not completed | 0 | 1 |
| Consent withdrawn by subject | - | 1 |

Period 3

| | |
|------------------------------|-------------------------------|
| Period 3 title | Treatment Period 2 (24 hours) |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--------------------------------------|
| Are arms mutually exclusive? | No |
| Arm title | Sequence 1: Ipren followed by Brufen |

Arm description:

Participants received Ipren in Treatment Period 1 and Brufen in Treatment Period 2. The washout period between the 24 hours treatment periods was at least 48 hours.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ipren |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received Ipren 200 milligram (mg) tablet orally once daily on day 1 of each treatment period.

| | |
|--|--------------------|
| Investigational medicinal product name | Brufen |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received Brufen 200 milligram (mg) tablet orally once daily on day 1 of each treatment period.

| | |
|------------------|--------------------------------------|
| Arm title | Sequence 2: Brufen followed by Ipren |
|------------------|--------------------------------------|

Arm description:

Participants received Brufen in Treatment Period 1 and Ipren in Treatment Period 2. The washout period between the 24 hours treatment periods was at least 48 hours.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ipren |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received Ipren 200 milligram (mg) tablet orally once daily on day 1 of each treatment period.

| | |
|--|--------------------|
| Investigational medicinal product name | Brufen |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received Brufen 200 milligram (mg) tablet orally once daily on day 1 of each treatment period.

| Number of subjects in period 3 | Sequence 1: Ipren followed by Brufen | Sequence 2: Brufen followed by Ipren |
|---------------------------------------|--------------------------------------|--------------------------------------|
| Started | 15 | 14 |
| Completed | 15 | 14 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Sequence 1: Ipren followed by Brufen |
|-----------------------|--------------------------------------|

Reporting group description:

Participants received Ipren in Treatment Period 1 and Brufen in Treatment Period 2. The washout period between the 24 hours treatment periods was at least 48 hours.

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Sequence 2: Brufen followed by Ipren |
|-----------------------|--------------------------------------|

Reporting group description:

Participants received Brufen in Treatment Period 1 and Ipren in Treatment Period 2. The washout period between the 24 hours treatment periods was at least 48 hours.

| Reporting group values | Sequence 1: Ipren followed by Brufen | Sequence 2: Brufen followed by Ipren | Total |
|---|--------------------------------------|--------------------------------------|-------|
| Number of subjects | 15 | 15 | 30 |
| Title for AgeCategorical Units: subjects | | | |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 15 | 15 | 30 |
| From 65 to 84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Title for AgeContinuous Units: years | | | |
| arithmetic mean | 29 | 27.3 | |
| standard deviation | ± 9.47 | ± 6.71 | - |
| Title for Gender Units: subjects | | | |
| Female | 5 | 7 | 12 |
| Male | 10 | 8 | 18 |

End points

End points reporting groups

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Sequence 1: Ipren followed by Brufen |
|-----------------------|--------------------------------------|

Reporting group description:

Participants received Ipren in Treatment Period 1 and Brufen in Treatment Period 2. The washout period between the 24 hours treatment periods was at least 48 hours.

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Sequence 2: Brufen followed by Ipren |
|-----------------------|--------------------------------------|

Reporting group description:

Participants received Brufen in Treatment Period 1 and Ipren in Treatment Period 2. The washout period between the 24 hours treatment periods was at least 48 hours.

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Sequence 1: Ipren followed by Brufen |
|-----------------------|--------------------------------------|

Reporting group description:

Participants received Ipren in Treatment Period 1 and Brufen in Treatment Period 2. The washout period between the 24 hours treatment periods was at least 48 hours.

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Sequence 2: Brufen followed by Ipren |
|-----------------------|--------------------------------------|

Reporting group description:

Participants received Brufen in Treatment Period 1 and Ipren in Treatment Period 2. The washout period between the 24 hours treatment periods was at least 48 hours.

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Sequence 1: Ipren followed by Brufen |
|-----------------------|--------------------------------------|

Reporting group description:

Participants received Ipren in Treatment Period 1 and Brufen in Treatment Period 2. The washout period between the 24 hours treatment periods was at least 48 hours.

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Sequence 2: Brufen followed by Ipren |
|-----------------------|--------------------------------------|

Reporting group description:

Participants received Brufen in Treatment Period 1 and Ipren in Treatment Period 2. The washout period between the 24 hours treatment periods was at least 48 hours.

| | |
|----------------------------|-------|
| Subject analysis set title | Ipren |
|----------------------------|-------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

This study was an open, single-dose, randomized, two-way cross-over study. Thirty (30) healthy male and female volunteers, aged between 18 and 50 years, inclusive, were included. Single doses of Ipren film coated tablet 200 mg and Brufen film coated tablet 200 mg were administered in a standardized mode, on two separated treatment visits. A washout period of at least 48 hours separated the treatments. After an overnight fast at the clinic, drug administration was started at about 8 am.

| | |
|----------------------------|--------|
| Subject analysis set title | Brufen |
|----------------------------|--------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

This study was an open, single-dose, randomized, two-way cross-over study. Thirty (30) healthy male and female volunteers, aged between 18 and 50 years, inclusive, were included. Single doses of Ipren film coated tablet 200 mg and Brufen film coated tablet 200 mg were administered in a standardized mode, on two separated treatment visits. A washout period of at least 48 hours separated the treatments. After an overnight fast at the clinic, drug administration was started at about 8 am.

Primary: Maximal Observed Plasma Concentration (C_{max}) of S-(+) Ibuprofen

| | |
|-----------------|--|
| End point title | Maximal Observed Plasma Concentration (C _{max}) of S-(+) Ibuprofen |
|-----------------|--|

End point description:

The C_{max} is the maximum observed plasma concentration.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose, 0.25, 0.5, 0.66, 0.83, 1, 1.16, 1.33, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 9 and 12 hours post-dose.

| End point values | Ipren | Brufen | | |
|--|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 29 | 29 | | |
| Units: microgram(s)/millilitre (ug/mL) | | | | |
| arithmetic mean (standard deviation) | 7.87 (± 1.83) | 9.8 (± 2.22) | | |

Statistical analyses

| Statistical analysis title | Cmax of S-(+) Ibuprofen comparison vs. Brufen |
|--|---|
| Statistical analysis description: | |
| Point and interval estimates are based on a linear model for ln-transformed Cmax data. Statistical model included covariate adjustments for period and sequence, and subject, nested within sequence as fixed effects. Number of subjects included in the cross-over analysis were 28. | |
| Comparison groups | Ipren v Brufen |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[1] |
| P-value | > 0.05 ^[2] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.233 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -0.302 |
| upper limit | -0.164 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.041 |

Notes:

[1] - For bioequivalence the 90% CI for the treatment difference (ln-scale), Ipren vs. Brufen, had to be contained in the interval from -0.223 to 0.223.

[2] - Exact value not calculated. Inference based on 90% confidence interval.

Primary: Area Under the Plasma Concentration Versus Time Curve from Start of Drug Administration Until the Time of the Last Measurable Plasma Concentration (AUCt) of S-(+) Ibuprofen

| | |
|-----------------|--|
| End point title | Area Under the Plasma Concentration Versus Time Curve from Start of Drug Administration Until the Time of the Last Measurable Plasma Concentration (AUCt) of S-(+) Ibuprofen |
|-----------------|--|

End point description:

The AUCt is the area under the plasma concentration-time curve from time zero to until the last measurable plasma concentration 't'.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Pre-dose, 0.25, 0.5, 0.66, 0.83, 1, 1.16, 1.33, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 9 and 12 hours post-dose.

| End point values | Ipren | Brufen | | |
|--|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 29 | 29 | | |
| Units: microgram/milliliter x hour (ug/mL x h) | | | | |
| arithmetic mean (standard deviation) | 37.67 (± 9.06) | 37.98 (± 10.03) | | |

Statistical analyses

| Statistical analysis title | AUCt of S-(+) Ibuprofen comparison vs. Brufen |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

Point and interval estimates are based on a linear model for ln-transformed AUCt data. Statistical model included covariate adjustments for period and sequence, and subject, nested within sequence as fixed effects. Number of subjects included in the cross-over analysis were 28.

| | |
|---|--------------------------------|
| Comparison groups | Ipren v Brufen |
| Number of subjects included in analysis | 58 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence ^[3] |
| P-value | < 0.05 ^[4] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.018 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -0.067 |
| upper limit | 0.031 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.029 |

Notes:

[3] - For bioequivalence the 90% CI for the treatment difference (ln-scale), Ipren vs. Brufen, had to be contained in the interval from -0.223 to 0.223.

[4] - Exact value not calculated. Inference based on 90% confidence interval.

Secondary: Maximal Observed Plasma Concentration (Cmax) of R-(-) Ibuprofen and Total Ibuprofen

| | |
|-----------------|---|
| End point title | Maximal Observed Plasma Concentration (Cmax) of R-(-) Ibuprofen and Total Ibuprofen |
|-----------------|---|

End point description:

The Cmax is the maximum observed plasma concentration.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose, 0.25, 0.5, 0.66, 0.83, 1, 1.16, 1.33, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 9 and 12 hours post-dose.

| End point values | Ipren | Brufen | | |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 29 | 28 | | |
| Units: microgram/milliliter (ug/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| R-(-) ibuprofen | 7.97 (± 2.46) | 9.67 (± 2.27) | | |
| Total ibuprofen | 15.78 (± 4.04) | 19.36 (± 4.15) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration Versus Time Curve from Start of Drug Administration Until the Time of the Last Measurable Plasma Concentration (AUCt) of R-(-) Ibuprofen and Total Ibuprofen

| | |
|-----------------|--|
| End point title | Area Under the Plasma Concentration Versus Time Curve from Start of Drug Administration Until the Time of the Last Measurable Plasma Concentration (AUCt) of R-(-) Ibuprofen and Total Ibuprofen |
|-----------------|--|

End point description:

The AUCt is the area under the plasma concentration-time curve from time zero to until the last measurable plasma concentration 't'.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose, 0.25, 0.5, 0.66, 0.83, 1, 1.16, 1.33, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 9 and 12 hours post-dose.

| End point values | Ipren | Brufen | | |
|--|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 29 | 28 | | |
| Units: microgram/milliliter x hour (ug/mL x h) | | | | |
| arithmetic mean (standard deviation) | | | | |
| R-(-) ibuprofen | 27.18 (± 7.71) | 27.77 (± 6.74) | | |
| Total ibuprofen | 65 (± 14.31) | 65.66 (± 13.95) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration Versus Time Curve from Start of Drug Administration Extrapolated to Infinity (AUCinfinity) for S-(+) Ibuprofen

| | |
|-----------------|--|
| End point title | Area Under the Plasma Concentration Versus Time Curve from Start of Drug Administration Extrapolated to Infinity (AUCinfinity) for S-(+) Ibuprofen |
|-----------------|--|

End point description:

The AUCinfinity is the area under the plasma concentration-time curve from time zero to infinite time, calculated as the sum of AUC(last) and C(last)/lambda(z); wherein AUC(last) is area under the plasma concentration-time curve from time zero to last quantifiable time, C(last) is the last observed quantifiable concentration, and lambda(z) is elimination rate constant.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose, 0.25, 0.5, 0.66, 0.83, 1, 1.16, 1.33, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 9 and 12 hours post-dose.

| End point values | Ipren | Brufen | | |
|--|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 29 | 29 | | |
| Units: microgram/milliliter x hour (ug/mL x h) | | | | |
| arithmetic mean (standard deviation) | 40.27 (± 10.54) | 40.12 (± 11.09) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration Versus Time Curve from Start of Drug Administration Extrapolated to Infinity (AUCinfinity) for R-(-) Ibuprofen and Total Ibuprofen

| | |
|-----------------|--|
| End point title | Area Under the Plasma Concentration Versus Time Curve from Start of Drug Administration Extrapolated to Infinity (AUCinfinity) for R-(-) Ibuprofen and Total Ibuprofen |
|-----------------|--|

End point description:

The AUCinfinity is the area under the plasma concentration-time curve from time zero to infinite time, calculated as the sum of AUC(last) and C(last)/lambda(z); wherein AUC(last) is area under the plasma concentration-time curve from time zero to last quantifiable time, C(last) is the last observed quantifiable concentration, and lambda(z) is elimination rate constant.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose, 0.25, 0.5, 0.66, 0.83, 1, 1.16, 1.33, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 9 and 12 hours post-dose.

| End point values | Ipren | Brufen | | |
|--|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 29 | 28 | | |
| Units: microgram/milliliter x hour (ug/mL x h) | | | | |
| arithmetic mean (standard deviation) | | | | |
| R-(-) ibuprofen | 27.59 (± 7.75) | 28.2 (± 6.75) | | |
| Total ibuprofen | 67.66 (± 15.4) | 67.8 (± 14.82) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Extrapolated Part of Area Under the Plasma Concentration Versus Time Curve from Start of Drug Administration Extrapolated to Infinity (AUC[infinity,ex]) for S-(+) Ibuprofen

| | |
|-----------------|--|
| End point title | Extrapolated Part of Area Under the Plasma Concentration Versus Time Curve from Start of Drug Administration Extrapolated to Infinity (AUC[infinity,ex]) for S-(+) Ibuprofen |
|-----------------|--|

End point description:

The AUC[infinity,ex] is calculated by dividing the difference of AUC(0-infinity) and AUC(0-last) by AUC(0-infinity), (AUC[0-infinity] - AUC[0-last])/AUC[0-infinity].

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose, 0.25, 0.5, 0.66, 0.83, 1, 1.16, 1.33, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 9 and 12 hours post-dose.

| End point values | Ipren | Brufen | | |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 29 | 29 | | |
| Units: percentage (%) | | | | |
| arithmetic mean (standard deviation) | 6 (± 3.5) | 5.1 (± 2.8) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Extrapolated Part of Area Under the Plasma Concentration Versus Time Curve from Start of Drug Administration Extrapolated to Infinity (AUC[infinity,ex]) for R-(-) Ibuprofen and Total Ibuprofen

| | |
|-----------------|--|
| End point title | Extrapolated Part of Area Under the Plasma Concentration Versus Time Curve from Start of Drug Administration Extrapolated to Infinity (AUC[infinity,ex]) for R-(-) Ibuprofen and Total Ibuprofen |
|-----------------|--|

End point description:

The AUC[infinity,ex] is calculated by dividing the difference of AUC(0-infinity) and AUC(0-last) by AUC(0-infinity), (AUC[0-infinity] - AUC[0-last])/AUC[0-infinity].

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose, 0.25, 0.5, 0.66, 0.83, 1, 1.16, 1.33, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 9 and 12 hours post-dose.

| End point values | Ipren | Brufen | | |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 29 | 28 | | |
| Units: percentage (%) | | | | |
| arithmetic mean (standard deviation) | | | | |
| R-(-) ibuprofen | 1.6 (± 1) | 1.6 (± 1.1) | | |
| Total ibuprofen | 3.7 (± 2.4) | 3 (± 1.9) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time at Which Maximal Plasma Concentration is Observed (Tmax) for S-(+) Ibuprofen

| | |
|---|---|
| End point title | Time at Which Maximal Plasma Concentration is Observed (Tmax) for S-(+) Ibuprofen |
| End point description: The Tmax is defined as actual sampling time to reach maximum observed S-(+) Ibuprofen concentration. | |
| End point type | Secondary |
| End point timeframe: Pre-dose, 0.25, 0.5, 0.66, 0.83, 1, 1.16, 1.33, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 9 and 12 hours post-dose. | |

| End point values | Ipren | Brufen | | |
|-------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 29 | 29 | | |
| Units: hours (h) | | | | |
| median (full range (min-max)) | 2.5 (1.17 to 4) | 1.33 (0.83 to 4) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time at Which Maximal Plasma Concentration is Observed (Tmax) for R-(-) Ibuprofen and Total Ibuprofen

| | |
|--|---|
| End point title | Time at Which Maximal Plasma Concentration is Observed (Tmax) for R-(-) Ibuprofen and Total Ibuprofen |
| End point description: The Tmax is defined as actual sampling time to reach maximum observed R-(-) Ibuprofen and Total Ibuprofen concentration. | |

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Pre-dose, 0.25, 0.5, 0.66, 0.83, 1, 1.16, 1.33, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 9 and 12 hours post-dose. | |

| End point values | Ipren | Brufen | | |
|-------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 29 | 28 | | |
| Units: hours (h) | | | | |
| median (full range (min-max)) | | | | |
| R-(-) ibuprofen | 2.5 (1.17 to 4) | 1.25 (0.83 to 4) | | |
| Total ibuprofen | 2.5 (1.17 to 4) | 1.25 (0.83 to 4) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Half Life (t_{1/2}) of S-(+) Ibuprofen

| | |
|--|---|
| End point title | Terminal Half Life (t _{1/2}) of S-(+) Ibuprofen |
| End point description: | |
| The elimination half-life (t _{1/2}) is the time measured for the plasma concentration to decrease by 1 half to its original concentration. It is associated with the terminal slope of the semi logarithmic drug concentration-time curve, and is calculated as 0.693/lambda(z). | |
| End point type | Secondary |
| End point timeframe: | |
| Pre-dose, 0.25, 0.5, 0.66, 0.83, 1, 1.16, 1.33, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 9 and 12 hours post-dose. | |

| End point values | Ipren | Brufen | | |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 29 | 29 | | |
| Units: hours (h) | | | | |
| arithmetic mean (standard deviation) | 2.47 (± 0.51) | 2.44 (± 0.36) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Half Life (t_{1/2}) of R-(-) Ibuprofen and Total Ibuprofen

| | |
|-----------------|---|
| End point title | Terminal Half Life (t _{1/2}) of R-(-) Ibuprofen and Total Ibuprofen |
|-----------------|---|

End point description:

The elimination half-life ($t_{1/2}$) is the time measured for the plasma concentration to decrease by 1 half to its original concentration. It is associated with the terminal slope of the semi logarithmic drug concentration-time curve, and is calculated as $0.693/\lambda(z)$.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose, 0.25, 0.5, 0.66, 0.83, 1, 1.16, 1.33, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 9 and 12 hours post-dose.

| End point values | Ipren | Brufen | | |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 29 | 28 | | |
| Units: hours (h) | | | | |
| arithmetic mean (standard deviation) | | | | |
| R-(-) ibuprofen | 1.61 (\pm 0.38) | 1.6 (\pm 0.39) | | |
| Total ibuprofen | 2.22 (\pm 0.43) | 2.12 (\pm 0.36) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Residence Time (MRT) for S-(+) Ibuprofen

| | |
|-----------------|---|
| End point title | Mean Residence Time (MRT) for S-(+) Ibuprofen |
|-----------------|---|

End point description:

The Mean Residence Time (MRT) is the average time at which the number of absorbed molecules reside in the body, after single-dose administration, and calculated as area under the first moment curve AUMC (0-infinity)/Area Under the Plasma Concentration-Time Curve AUC (0-infinity), where AUMC (0-infinity) is area under the plasma concentration-time first moment curve from time zero to infinite time and AUC (0-infinity) is the area under the plasma concentration-time curve from time zero to infinite time.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose, 0.25, 0.5, 0.66, 0.83, 1, 1.16, 1.33, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 9 and 12 hours post-dose.

| End point values | Ipren | Brufen | | |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 29 | 29 | | |
| Units: hours (h) | | | | |
| arithmetic mean (standard deviation) | 5.23 (\pm 0.98) | 4.58 (\pm 0.98) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Residence Time (MRT) for R-(-) Ibuprofen and Total Ibuprofen

| | |
|-----------------|---|
| End point title | Mean Residence Time (MRT) for R-(-) Ibuprofen and Total Ibuprofen |
|-----------------|---|

End point description:

The Mean Residence Time (MRT) is the average time at which the number of absorbed molecules reside in the body, after single-dose administration, and calculated as area under the first moment curve AUMC (0-infinity)/Area Under the Plasma Concentration-Time Curve AUC (0-infinity), where AUMC (0-infinity) is area under the plasma concentration-time first moment curve from time zero to infinite time and AUC (0-infinity) is the area under the plasma concentration-time curve from time zero to infinite time.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose, 0.25, 0.5, 0.66, 0.83, 1, 1.16, 1.33, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 9 and 12 hours post-dose.

| End point values | Ipren | Brufen | | |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 29 | 28 | | |
| Units: hours (h) | | | | |
| arithmetic mean (standard deviation) | | | | |
| R-(-) ibuprofen | 3.66 (± 0.66) | 3.26 (± 0.72) | | |
| Total ibuprofen | 4.57 (± 0.84) | 4.01 (± 0.89) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Elimination Rate Constant for S-(+) Ibuprofen

| | |
|-----------------|--|
| End point title | Terminal Elimination Rate Constant for S-(+) Ibuprofen |
|-----------------|--|

End point description:

Lambda(z) is first-order elimination rate constant associated with the terminal portion of the curve, determined as the negative slope of the terminal log-linear phase of the drug concentration-time curve.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose, 0.25, 0.5, 0.66, 0.83, 1, 1.16, 1.33, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 9 and 12 hours post-dose.

| End point values | Ipren | Brufen | | |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 29 | 29 | | |
| Units: 1/hour (1/h) | | | | |
| arithmetic mean (standard deviation) | 0.29 (± 0.07) | 0.29 (± 0.04) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Elimination Rate Constant for R-(-) Ibuprofen and Total Ibuprofen

| | |
|-----------------|--|
| End point title | Terminal Elimination Rate Constant for R-(-) Ibuprofen and Total Ibuprofen |
|-----------------|--|

End point description:

Lambda(z) is first-order elimination rate constant associated with the terminal portion of the curve, determined as the negative slope of the terminal log-linear phase of the drug concentration-time curve.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose, 0.25, 0.5, 0.66, 0.83, 1, 1.16, 1.33, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 9 and 12 hours post-dose.

| End point values | Ipren | Brufen | | |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 29 | 28 | | |
| Units: 1/hour (1/h) | | | | |
| arithmetic mean (standard deviation) | | | | |
| R-(-) ibuprofen | 0.46 (± 0.13) | 0.46 (± 0.1) | | |
| Total ibuprofen | 0.32 (± 0.07) | 0.34 (± 0.06) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of Adverse Events

| | |
|-----------------|------------------------------|
| End point title | Occurrence of Adverse Events |
|-----------------|------------------------------|

End point description:

Serious adverse events required immediate notification within 24 hours to the sponsor or its designated representative beginning from the time that the subject provides informed consent, which was obtained prior to the subject's participation in the clinical study (i.e. prior to undergoing any study-related procedure and/or receiving investigational product), through and including 30 calendar days after the last administration of the investigational product. Any serious adverse event occurring any time after the reporting period was to be promptly reported if a causal relationship to investigational product was suspected.

Adverse events (serious and non-serious) were recorded on the CRF from the time the subjects had taken at least one dose of study treatment through last subject visit.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Serious adverse events require notification within 24 hours to the sponsor or its designated representative beginning from the time that the subject provides informed consent, through and including 30 calendar days after the last administration.

| End point values | Ipren | Brufen | | |
|---------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 29 | 30 | | |
| Units: Number of Adverse Events | | | | |
| Serious adverse events | 0 | 0 | | |
| Non serious adverse events | 6 | 11 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events required notification within 24 hours to the sponsor or its designated representative beginning from the time that the subject provides informed consent, through and including 30 calendar days after the last administration.

Adverse event reporting additional description:

The investigator obtained and recorded on the eCRF/CRF all observed or volunteered adverse events. For all adverse events, the investigator pursued and obtained information adequate to determine both the outcome of the adverse event and whether it met the criteria for classification as a serious adverse event.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 16.0 |

Reporting groups

| | |
|-----------------------|--------|
| Reporting group title | Brufen |
|-----------------------|--------|

Reporting group description:

Ibuprofen (Brufen) Film Coated Tablet 200 mg

| | |
|-----------------------|-------|
| Reporting group title | Ipren |
|-----------------------|-------|

Reporting group description:

Ibuprofen (Ipren) Film Coated Tablet 200 mg

| Serious adverse events | Brufen | Ipren | |
|---|----------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 30 (0.00%) | 0 / 29 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Brufen | Ipren | |
|---|-----------------|-----------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 9 / 30 (30.00%) | 6 / 29 (20.69%) | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 7 / 30 (23.33%) | 6 / 29 (20.69%) | |
| occurrences (all) | 7 | 6 | |
| Gastrointestinal disorders | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| Nausea | | | |
| subjects affected / exposed | 2 / 30 (6.67%) | 0 / 29 (0.00%) | |
| occurrences (all) | 2 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported