



Clinical trial results:

An Open-label, Randomised, Three -Way, Cross-Over Study to Assess the Pharmacokinetics, Safety and Tolerability of Two Formulations of RBP-6300 10mg in Healthy Volunteers under a Naltrexone Block in the Presence and Absence of Food

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2012-002408-42 |
| Trial protocol | GB |
| Global end of trial date | 23 December 2013 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 06 July 2016 |
| First version publication date | 06 August 2015 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | RB-UK-12-0004 |
|-----------------------|---------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Reckitt Benckiser Pharmaceuticals, Inc |
| Sponsor organisation address | 10710 Midlothian Turnpike, Suite 430, Richmond, VA, United States, 23235 |
| Public contact | Director of Clinical Operations, Reckitt Benckiser Pharmaceuticals Inc., 01 804-594-2029, |
| Scientific contact | Director of Clinical Operations, Reckitt Benckiser Pharmaceuticals Inc., 01 804-594-2029, |

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 | 27 August 2014 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 23 December 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the relative bioavailability of buprenorphine after oral administration of RBP 6300 (Formulation A) 10 mg as compared to RBP 6300 (Formulation B) 10 mg, when administered in the fasted state.

To assess the relative bioavailability of buprenorphine after oral administration of RBP 6300 (Formulation A) 10 mg to subjects who have been fed a high-fat breakfast as compared to fasted.

Protection of trial subjects:

The Investigator was responsible for ensuring that the clinical study was performed in accordance with the protocol, current International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements. GCP is an international, ethical, and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides the public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, 1996, and that the clinical study data are credible.

All informed consent documents and other documents used in the conduct of the study were approved by the IEC. Subjects were given consent documents to review before attending Screening. Prior to the Screening procedures, a medically qualified associate explained to each subject in a group setting the nature of the study, its purpose, procedures, expected duration, alternative therapies available, and the benefits and risks involved in study participation.

Subjects were informed of their right to withdraw from the study at any time without prejudice.

After this explanation, and before any study-specific procedures were performed, the subject voluntarily signed and dated the ICF to indicate their wish to participate in the study. The Investigator or designated subinvestigator also signed and dated the ICF. The time (hour and minute) the ICF was signed was also recorded by the subject and the person obtaining consent from the subject.

Prior to participation in the study, the subject received a copy of the signed and dated ICF along with an emergency card with contact information for the Investigator and site staff in the event of a medical emergency during the study.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 27 September 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 Kingdom: 50 |
| Worldwide total number of subjects | 50 |
| EEA total number of subjects | 50 |

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) | 0 |
| Adults (18-64 years) | 50 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 106 subjects were screened and 52 approved for participation. Two approved subjects were designated alternates who were not randomized or dosed.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|-----------|--------------|
| Arm title | All Subjects |
|-----------|--------------|

Arm description:

Subjects were randomized to 1 of 6 treatment arm combinations in this cross-over study. The three treatments (given in the assigned combination order) were 1). RBP-6300 Formulation A (10 mg buprenorphine hemiadipate HCl/10 mg naloxone HCl dihydrate) administered as an oral tablet after an overnight fast of at least 10 hours. 2). RBP-6300 Formulation B (10 mg buprenorphine hemiadipate HCl/10 mg naloxone HCl dihydrate) administered as an oral tablet after an overnight fast of at least 10 hours. 3). RBP-6300 Formulation A administered as an oral tablet within 30 minutes of starting and completing a high-fat breakfast following an overnight fast of at least 10 hours. A single oral tablet of each treatment was given at the beginning of each treatment period followed by a 14 day washout prior to starting the next treatment period.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | RBP-6300 Formulation A |
| Investigational medicinal product code | |
| Other name | buprenorphine hemiadipate HCl , naloxone HCl dihydrate |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Each Formula A RBP-6300 tablet contains 10 mg buprenorphine hemiadipate HCl [7.20 mg buprenorphine free base] and 10 mg naloxone HCl dihydrate [8.18 mg naloxone free base]. Each dose was a single tablet taken orally in the am, either following a 10 hour fast or following a high-fat breakfast.

Formula A has the same amount of buprenorphine and naloxone as Formula B. However Formula A contains fewer insoluble excipients than Formula B, thus reducing the potential harm to abusers.

| | |
|--|--|
| Investigational medicinal product name | RBP-6300 Formulation B |
| Investigational medicinal product code | |
| Other name | buprenorphine hemiadipate HCl , naloxone HCl dihydrate |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Each Formula B RBP-6300 tablet contains 10 mg buprenorphine hemiadipate HCl [7.20 mg buprenorphine free base] and 10 mg naloxone HCl dihydrate [8.18 mg naloxone free base]. Each dose was a single tablet taken orally in the am following a 10 hour fast.

Formula B has the same amount of buprenorphine and naloxone as Formula A. Formula B has been used in all previous clinical trials with RBP-6300 and contains more insoluble excipients than Formula A.

| | |
|--|------------|
| Investigational medicinal product name | naltrexone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Naltrexone was administered both pre- and post-RBP-6300 dosing in order to minimize the occurrence of unacceptable AEs (eg, decreased respiration, nausea) often associated with the administration of buprenorphine in opiate-naïve, healthy subjects.

Naltrexone 100 mg was given at 13 hours [\pm 1 hour] and at 2 hours [\pm 15 minutes] predose. It was also given 50 mg at 12 hours [\pm 1 hour] and 24 hours [\pm 1 hour] post dose.

| Number of subjects in period 1 | All Subjects |
|---------------------------------------|--------------|
| Started | 50 |
| RBP-6300 Formulation A - Fasting | 47 |
| RBP-6300 Formulation B - Fasting | 47 |
| RBP-6300 Formulation A - High Fat | 44 |
| Completed | 41 |
| Not completed | 9 |
| Consent withdrawn by subject | 1 |
| Adverse event, non-fatal | 6 |
| Not specified | 2 |

Baseline characteristics

Reporting groups

| | |
|--|---------------|
| Reporting group title | Overall trial |
| Reporting group description: | |
| All subjects regardless of the order of the study interventions assigned in this cross-over trial. | |

| Reporting group values | Overall trial | Total | |
|---|---------------|-------|--|
| Number of subjects | 50 | 50 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 50 | 50 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 34.1 | | |
| full range (min-max) | 19 to 55 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 16 | 16 | |
| Male | 34 | 34 | |
| Race | | | |
| Units: Subjects | | | |
| White | 50 | 50 | |
| Black or African American | 0 | 0 | |
| Asian | 0 | 0 | |
| American Indian or Alaska Native | 0 | 0 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Other | 0 | 0 | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 1 | 1 | |
| Not Hispanic or Latino | 49 | 49 | |
| Weight | | | |
| Units: kg | | | |
| arithmetic mean | 75.72 | | |
| full range (min-max) | 54.8 to 96.4 | - | |
| Height | | | |
| Units: cm | | | |
| arithmetic mean | 173 | | |
| full range (min-max) | 149 to 191 | - | |
| Body Mass Index (BMI) | | | |
| Units: kg/m ² | | | |
| arithmetic mean | 25.2 | | |
| full range (min-max) | 18.5 to 29.3 | - | |

End points

End points reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | All Subjects |
|-----------------------|--------------|

Reporting group description:

Subjects were randomized to 1 of 6 treatment arm combinations in this cross-over study. The three treatments (given in the assigned combination order) were 1). RBP-6300 Formulation A (10 mg buprenorphine hemiadipate HCl/10 mg naloxone HCl dihydrate) administered as an oral tablet after an overnight fast of at least 10 hours. 2). RBP-6300 Formulation B (10 mg buprenorphine hemiadipate HCl/10 mg naloxone HCl dihydrate) administered as an oral tablet after an overnight fast of at least 10 hours. 3). RBP-6300 Formulation A administered as an oral tablet within 30 minutes of starting and completing a high-fat breakfast following an overnight fast of at least 10 hours. A single oral tablet of each treatment was given at the beginning of each treatment period followed by a 14 day washout prior to starting the next treatment period.

| | |
|----------------------------|----------------------------------|
| Subject analysis set title | RBP-6300 Formulation A - Fasting |
|----------------------------|----------------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

RBP-6300 Formulation A (10 mg buprenorphine hemiadipate HCl/10 mg naloxone HCl dihydrate) administered as an oral tablet after an overnight fast of at least 10 hours.

| | |
|----------------------------|----------------------------------|
| Subject analysis set title | RBP-6300 Formulation B - Fasting |
|----------------------------|----------------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

RBP-6300 Formulation B (10 mg buprenorphine hemiadipate HCl/10 mg naloxone HCl dihydrate) administered as an oral tablet after an overnight fast of at least 10 hours.

| | |
|----------------------------|-----------------------------------|
| Subject analysis set title | RBP-6300 Formulation A - High Fat |
|----------------------------|-----------------------------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

RBP-6300 Formulation A administered as an oral tablet within 30 minutes of starting and completing a high-fat breakfast following an overnight fast of at least 10 hours.

Primary: Buprenorphine: Area under the plasma concentration-time curve from time 0 to 72 hours post dose (AUC0-72), AUC0-96, AUCinf, and AUClast

| | |
|-----------------|---|
| End point title | Buprenorphine: Area under the plasma concentration-time curve from time 0 to 72 hours post dose (AUC0-72), AUC0-96, AUCinf, and AUClast |
|-----------------|---|

End point description:

PK parameters were calculated from the concentration-time data using noncompartmental methods (Phoenix® WinNonlin®, version 6.3) and actual sampling times. The PK parameters for any subjects who experienced emesis within 4 hours of administration of study treatment were excluded from the descriptive statistics and statistical analysis. Concentration-time data for subjects with quantifiable predose concentrations less than 5% of the respective C_{max} were included in the PK and statistical analysis without adjustment. Data for subjects with quantifiable predose concentrations greater than 5% of the respective C_{max} were excluded from the PK and statistical analysis.

AUC0-96: Area under the plasma concentration-time curve from time 0 to 96 hours post dose

AUCinf: Area under the plasma concentration-time curve from time 0 extrapolated to Infinity post dose

AUClast: Area under the plasma concentration-time curve from time 0 to the last quantifiable concentration

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

End point timeframe:

Predose and 5 minutes and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 (Day 2), 36, 48 (Day 3), 72 hours (Day 4), post dose. Dosing days included Day 1, Day 22 and Day 43

| End point values | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat | |
|--------------------------------------|--|--|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 43 ^[1] | 44 ^[2] | 43 ^[3] | |
| Units: hr*mg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| AUC0-72 | 12.205 (± 4.9607) | 12.295 (± 5.6173) | 15.932 (± 6.3917) | |
| AUC0-96 | 13.535 (± 5.4959) | 13.54 (± 6.1411) | 17.581 (± 7.1447) | |
| AUCinf | 16.279 (± 6.0194) | 16.7 (± 7.0443) | 21.881 (± 8.0195) | |
| AUClast | 14.181 (± 6.3366) | 14.191 (± 6.9789) | 18.743 (± 8.0898) | |

Notes:

[1] - PK population

AUCinf: # subjects was 38

[2] - PK population

AUCinf: # subjects was 36

[3] - PK population

AUCinf: # subjects was 38

Statistical analyses

| Statistical analysis title | AUC0-72: Formula A Fasting to Formula B Fasting |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

Comparison of the natural log-transformed AUC tests was performed using an analysis of variance (ANOVA) model with sequence, subject nested within sequence, treatment, and period as fixed effects.

subjects in this analysis: 87 represents the sum of subjects contributing data in the two arms, not unique subjects.

| | |
|---|---|
| Comparison groups | RBP-6300 Formulation A - Fasting v RBP-6300 Formulation B - Fasting |
| Number of subjects included in analysis | 87 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Geometric LSMean ratio |
| Point estimate | 1.0124 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.9524 |
| upper limit | 1.0761 |

| Statistical analysis title | AUC0-72: Formula A High Fat to Formula A Fasting |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

Comparison of the natural log-transformed AUC tests was performed using an analysis of variance (ANOVA) model with sequence, subject nested within sequence, treatment, and period as fixed effects.

subjects in this analysis: 86 represents the sum of subjects contributing data in the two arms, not unique subjects.

| | |
|-------------------|--|
| Comparison groups | RBP-6300 Formulation A - Fasting v RBP-6300 Formulation A - High Fat |
|-------------------|--|

| | |
|---|------------------------|
| Number of subjects included in analysis | 86 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Geometric LSMean ratio |
| Point estimate | 1.323 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 1.2433 |
| upper limit | 1.4079 |

| | |
|-----------------------------------|---|
| Statistical analysis title | AUC0-92: Formula A Fasting to Formula B Fasting |
|-----------------------------------|---|

Statistical analysis description:

Comparison of the natural log-transformed AUC tests was performed using an analysis of variance (ANOVA) model with sequence, subject nested within sequence, treatment, and period as fixed effects.

subjects in this analysis: 87 represents the sum of subjects contributing data in the two arms, not unique subjects.

| | |
|---|---|
| Comparison groups | RBP-6300 Formulation A - Fasting v RBP-6300 Formulation B - Fasting |
| Number of subjects included in analysis | 87 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Geometric LSMean ratio |
| Point estimate | 1.011 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.9514 |
| upper limit | 1.0744 |

| | |
|-----------------------------------|--|
| Statistical analysis title | AUC0-92: Formula A High Fat to Formula A Fasting |
|-----------------------------------|--|

Statistical analysis description:

Comparison of the natural log-transformed AUC tests was performed using an analysis of variance (ANOVA) model with sequence, subject nested within sequence, treatment, and period as fixed effects.

subjects in this analysis: 86 represents the sum of subjects contributing data in the two arms, not unique subjects.

| | |
|---|--|
| Comparison groups | RBP-6300 Formulation A - Fasting v RBP-6300 Formulation A - High Fat |
| Number of subjects included in analysis | 86 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Geometric LSMean ratio |
| Point estimate | 1.3131 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 1.2344 |
| upper limit | 1.3969 |

| | |
|-----------------------------------|--|
| Statistical analysis title | AUCinf: Formula A Fasting to Formula B Fasting |
|-----------------------------------|--|

Statistical analysis description:

Comparison of the natural log-transformed AUC tests was performed using an analysis of variance (ANOVA) model with sequence, subject nested within sequence, treatment, and period as fixed effects.

subjects in this analysis: 74 represents the sum of subjects contributing data in the two arms, not unique subjects. Note there were fewer subjects in each arm of the AUCinf calculation than in the other AUC measurements.

| | |
|---|---|
| Comparison groups | RBP-6300 Formulation A - Fasting v RBP-6300 Formulation B - Fasting |
| Number of subjects included in analysis | 87 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Geometric LSMean ratio |
| Point estimate | 1.0264 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.9539 |
| upper limit | 1.1043 |

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|-----------------------------------|---|
| Statistical analysis title | AUCinf: Formula A High Fat to Formula A Fasting |
|-----------------------------------|---|

Statistical analysis description:

Comparison of the natural log-transformed AUC tests was performed using an analysis of variance (ANOVA) model with sequence, subject nested within sequence, treatment, and period as fixed effects.

subjects in this analysis: 76 represents the sum of subjects contributing data in the two arms, not unique subjects. Note there were fewer subjects in each arm of the AUCinf calculation than in the other AUC measurements.

| | |
|---|--|
| Comparison groups | RBP-6300 Formulation A - Fasting v RBP-6300 Formulation A - High Fat |
| Number of subjects included in analysis | 86 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Geometric LSMean ratio |
| Point estimate | 1.3321 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 1.2382 |
| upper limit | 1.4332 |

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|--|---|
| Statistical analysis title | AUClast: Formula A Fasting to Formula B Fasting |
| Statistical analysis description: | |
| Comparison of the natural log-transformed AUC tests was performed using an analysis of variance (ANOVA) model with sequence, subject nested within sequence, treatment, and period as fixed effects. | |
| # subjects in this analysis: 87 represents the sum of subjects contributing data in the two arms, not unique subjects. | |
| Comparison groups | RBP-6300 Formulation A - Fasting v RBP-6300 Formulation B - Fasting |
| Number of subjects included in analysis | 87 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Geometric LSMean ratio |
| Point estimate | 1.012 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.9451 |
| upper limit | 1.0836 |

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|--|--|
| Statistical analysis title | AUClast: Formula A High Fat to Formula A Fasting |
| Statistical analysis description: | |
| Comparison of the natural log-transformed AUC tests was performed using an analysis of variance (ANOVA) model with sequence, subject nested within sequence, treatment, and period as fixed effects. | |
| # subjects in this analysis: 86 represents the sum of subjects contributing data in the two arms, not unique subjects. | |
| Comparison groups | RBP-6300 Formulation A - Fasting v RBP-6300 Formulation A - High Fat |
| Number of subjects included in analysis | 86 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Geometric LSMean ratio |
| Point estimate | 1.345 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 1.2546 |
| upper limit | 1.4418 |

Secondary: Buprenorphine: Apparent clearance (CL/F)

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|---|--|
| End point title | Buprenorphine: Apparent clearance (CL/F) |
| End point description: | |
| PK parameters were calculated from the concentration-time data using noncompartmental methods (Phoenix® WinNonlin®, version 6.3) and actual sampling times. PK parameters for any subjects who experienced emesis within 4 hours of | |

administration of study treatment were excluded from the descriptive statistics and statistical analysis. Concentration-time data for subjects with quantifiable predose concentrations less than 5% of the respective C_{max} were included in the PK and statistical analysis without adjustment. Data for subjects with quantifiable predose concentrations greater than 5% of the respective C_{max} were excluded from the PK and statistical analysis.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Predose and 5 minutes and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 (Day 2), 36, 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), and 144 hours (Day 7) post dose. Dosing days included Day 1, Day 22 and Day 43 | |

| End point values | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat | |
|--------------------------------------|--|--|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 38 ^[4] | 36 ^[5] | 38 ^[6] | |
| Units: L/hour | | | | |
| arithmetic mean (standard deviation) | 519.99 (± 200.807) | 521.46 (± 223.406) | 382.43 (± 143.278) | |

Notes:

[4] - PK population

[5] - PK population

[6] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: Buprenorphine: Maximum observed plasma concentration (C_{max})

| | |
|-----------------|--|
| End point title | Buprenorphine: Maximum observed plasma concentration (C _{max}) |
|-----------------|--|

End point description:

PK parameters were calculated from the concentration-time data using noncompartmental methods (Phoenix® WinNonlin®, version 6.3) and actual sampling times. PK parameters for any subjects who experienced emesis within 4 hours of administration of study treatment were excluded from the descriptive statistics and statistical analysis. Concentration-time data for subjects with quantifiable predose concentrations less than 5% of the respective C_{max} were included in the PK and statistical analysis without adjustment. Data for subjects with quantifiable predose concentrations greater than 5% of the respective C_{max} were excluded from the PK and statistical analysis.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Predose and 5 minutes and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 (Day 2), 36, 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), and 144 hours (Day 7) post dose. Dosing days included Day 1, Day 22 and Day 43 | |

| End point values | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat | |
|--------------------------------------|--|--|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 43 ^[7] | 44 ^[8] | 43 ^[9] | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 1.545 (± 1.0075) | 1.383 (± 0.9194) | 1.466 (± 0.9581) | |

Notes:

[7] - PK population

[8] - PK population

[9] - PK population

Statistical analyses

| Statistical analysis title | Cmax: Formula A Fasting to Formula B Fasting |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

Comparison of the natural log-transformed Cmax tests was performed using an analysis of variance (ANOVA) model with sequence, subject nested within sequence, treatment, and period as fixed effects.

subjects in this analysis: 87 represents the sum of subjects contributing data in the two arms, not unique subjects.

| | |
|---|---|
| Comparison groups | RBP-6300 Formulation A - Fasting v RBP-6300 Formulation B - Fasting |
| Number of subjects included in analysis | 87 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Geometric LSMean ratio |
| Point estimate | 1.1243 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.9678 |
| upper limit | 1.3061 |

| Statistical analysis title | Cmax: Formula A High Fat to Formula A Fasting |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

Comparison of the natural log-transformed Cmax tests was performed using an analysis of variance (ANOVA) model with sequence, subject nested within sequence, treatment, and period as fixed effects.

subjects in this analysis: 86 represents the sum of subjects contributing data in the two arms, not unique subjects.

| | |
|---|--|
| Comparison groups | RBP-6300 Formulation A - Fasting v RBP-6300 Formulation A - High Fat |
| Number of subjects included in analysis | 86 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Geometric LSMean ratio |
| Point estimate | 0.9475 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.8134 |
| upper limit | 1.1036 |

Secondary: Buprenorphine: Time to maximum plasma concentration (Tmax)

| | |
|-----------------|--|
| End point title | Buprenorphine: Time to maximum plasma concentration (Tmax) |
|-----------------|--|

End point description:

PK parameters were calculated from the concentration-time data using noncompartmental methods (Phoenix® WinNonlin®, version 6.3) and actual sampling times. Concentration-time data for subjects with quantifiable predose concentrations less than 5% of the respective Cmax were included in the PK and statistical analysis without adjustment. Data for subjects with quantifiable predose concentrations greater than 5% of the respective Cmax were excluded from the PK and statistical analysis.

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

End point timeframe:

Predose and 5 minutes and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 (Day 2), 36, 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), and 144 hours (Day 7) post dose. Dosing days included Day 1, Day 22 and Day 43

| End point values | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat | |
|-------------------------------|----------------------------------|----------------------------------|-----------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 43 ^[10] | 44 ^[11] | 43 ^[12] | |
| Units: hour | | | | |
| median (full range (min-max)) | 0.75 (0.5 to 4) | 0.75 (0.25 to 3) | 2 (0.5 to 10) | |

Notes:

[10] - PK population

[11] - PK population

[12] - PK population

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Tmax: Formula A Fasting to Formula B Fasting |
|----------------------------|--|

Statistical analysis description:

Differences in Tmax across treatments were tested using the nonparametric Wilcoxon signed rank test. Additionally, a 95% nonparametric CI was constructed for the median difference in the Tmax values based on the Hodges-Lehmann estimates.

subjects in this analysis: 87 represents the sum of subjects contributing data in the two arms, not unique subjects.

| | |
|-------------------|---|
| Comparison groups | RBP-6300 Formulation A - Fasting v RBP-6300 Formulation B - Fasting |
|-------------------|---|

| | |
|---|----------------------------------|
| Number of subjects included in analysis | 87 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.7916 ^[13] |
| Method | Wilcoxon (Mann-Whitney) |
| Parameter estimate | Median difference (final values) |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.125 |
| upper limit | 0.125 |

Notes:

[13] - Statistical tests conducted were two-sided at an α level of 0.05.

| | |
|-----------------------------------|---|
| Statistical analysis title | Tmax: Formula A High Fat to Formula A Fasting |
|-----------------------------------|---|

Statistical analysis description:

Differences in Tmax across treatments were tested using the nonparametric Wilcoxon signed rank test. Additionally, a 95% nonparametric CI was constructed for the median difference in the Tmax values based on the Hodges-Lehmann estimates.

subjects in this analysis: 86 represents the sum of subjects contributing data in the two arms, not unique subjects.

| | |
|---|--|
| Comparison groups | RBP-6300 Formulation A - Fasting v RBP-6300 Formulation A - High Fat |
| Number of subjects included in analysis | 86 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.0001 ^[14] |
| Method | Wilcoxon (Mann-Whitney) |
| Parameter estimate | Median difference (final values) |
| Point estimate | 1.375 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.75 |
| upper limit | 2 |

Notes:

[14] - Statistical tests conducted were two-sided at an α level of 0.05.

Secondary: Buprenorphine: Apparent volume of distribution (Vz/F)

| | |
|-----------------|---|
| End point title | Buprenorphine: Apparent volume of distribution (Vz/F) |
|-----------------|---|

End point description:

PK parameters were calculated from the concentration-time data using noncompartmental methods (Phoenix® WinNonlin®, version 6.3) and actual sampling times. PK parameters for any subjects who experienced emesis within 4 hours of administration of study treatment were excluded from the descriptive statistics and statistical analysis. Concentration-time data for subjects with quantifiable predose concentrations less than 5% of the respective Cmax were included in the PK and statistical analysis without adjustment. Data for subjects with quantifiable predose concentrations greater than 5% of the respective Cmax were excluded from the PK and statistical analysis.

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

End point timeframe:

Predose and 5 minutes and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 (Day 2), 36, 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), and 144 hours (Day 7) post dose. Dosing days included Day

| End point values | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat | |
|--------------------------------------|--|--|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 38 ^[15] | 36 ^[16] | 38 ^[17] | |
| Units: Liters | | | | |
| arithmetic mean (standard deviation) | 26416.58 (± 9137.672) | 26594.9 (± 9681.089) | 20800.46 (± 8590.982) | |

Notes:

[15] - PK population

[16] - PK population

[17] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: Buprenorphine: Terminal phase half-life (T1/2)

| | |
|-----------------|--|
| End point title | Buprenorphine: Terminal phase half-life (T1/2) |
|-----------------|--|

End point description:

PK parameters were calculated from the concentration-time data using noncompartmental methods (Phoenix® WinNonlin®, version 6.3) and actual sampling times. PK parameters for any subjects who experienced emesis within 4 hours of administration of study treatment were excluded from the descriptive statistics and statistical analysis. Concentration-time data for subjects with quantifiable predose concentrations less than 5% of the respective C_{max} were included in the PK and statistical analysis without adjustment. Data for subjects with quantifiable predose concentrations greater than 5% of the respective C_{max} were excluded from the PK and statistical analysis.

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

End point timeframe:

Predose and 5 minutes and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 (Day 2), 36, 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), and 144 hours (Day 7) post dose. Dosing days included Day 1, Day 22 and Day 43

| End point values | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat | |
|--------------------------------------|--|--|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 42 ^[18] | 43 ^[19] | 43 ^[20] | |
| Units: hour | | | | |
| arithmetic mean (standard deviation) | 39.352 (± 15.3397) | 42.475 (± 19.5276) | 42.513 (± 20.3092) | |

Notes:

[18] - PK population

[19] - PK population

[20] - PK population

Statistical analyses

| | |
|---|---|
| Statistical analysis title | T1/2: Formula A Fasting to Formula B Fasting |
| Statistical analysis description: | |
| Comparison of observed values for T1/2 was performed using an analysis of variance (ANOVA) model with sequence, subject nested within sequence, treatment, and period as fixed effects. # subjects in this analysis: 85 represents the sum of subjects contributing data in the two arms, not unique subjects. | |
| Comparison groups | RBP-6300 Formulation A - Fasting v RBP-6300 Formulation B - Fasting |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Difference of LSMean |
| Point estimate | -2.667 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -9.212 |
| upper limit | 3.879 |

| | |
|---|--|
| Statistical analysis title | T1/2: Formula A High Fat to Formula A Fasting |
| Statistical analysis description: | |
| Comparison of observed values for T1/2 was performed using an analysis of variance (ANOVA) model with sequence, subject nested within sequence, treatment, and period as fixed effects. # subjects in this analysis: 85 represents the sum of subjects contributing data in the two arms, not unique subjects. | |
| Comparison groups | RBP-6300 Formulation A - Fasting v RBP-6300 Formulation A - High Fat |
| Number of subjects included in analysis | 85 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Difference of LSMean |
| Point estimate | 2.882 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -3.735 |
| upper limit | 9.5 |

Secondary: Naloxone: Area under the plasma concentration-time curve from time 0 to 72 hours post dose (AUC0-72), AUC0-96, AUCinf, and AUClast

| | |
|-----------------|--|
| End point title | Naloxone: Area under the plasma concentration-time curve from time 0 to 72 hours post dose (AUC0-72), AUC0-96, AUCinf, and AUClast |
|-----------------|--|

End point description:

PK parameters were calculated from the concentration-time data using noncompartmental methods (Phoenix® WinNonlin®, version 6.3) and actual sampling times. The PK parameters for any subjects who experienced emesis within 4 hours of administration of study treatment were excluded from the descriptive statistics and statistical analysis. Concentration-time data for subjects with quantifiable predose concentrations less than 5% of the respective C_{max} were included in the PK and statistical analysis without adjustment. Data for subjects with quantifiable predose concentrations greater than 5% of the respective C_{max} were excluded from

the PK and statistical analysis.

AUC0-96: Area under the plasma concentration-time curve from time 0 to 96 hours post dose

AUCinf: Area under the plasma concentration-time curve from time 0 extrapolated to Infinity post dose

AUClast: Area under the plasma concentration-time curve from time 0 to the last quantifiable concentration

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

End point timeframe:

Predose and 5 minutes and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 (Day 2), 36, 48 (Day 3), 72 hours (Day 4), post dose. Dosing days included Day 1, Day 22 and Day 43

| End point values | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat | |
|--------------------------------------|--|--|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 43 ^[21] | 43 ^[22] | 42 ^[23] | |
| Units: hr*pg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| AUC0-72 (n=43, 43, 42) | 536.882 (± 379.091) | 536.354 (± 380.102) | 621.068 (± 350.954) | |
| AUC0-96 (n=43, 43, 42) | 541.186 (± 382.039) | 541.72 (± 383.261) | 624.075 (± 351.424) | |
| AUCinf (n=40, 39, 41) | 558.988 (± 392.757) | 532.576 (± 384.951) | 630.683 (± 354.287) | |
| AUClast (n=43, 43, 42) | 512.556 (± 369.972) | 514.805 (± 384.814) | 600.107 (± 351.611) | |

Notes:

[21] - PK population

AUCinf: # subjects was 40

[22] - PK population

AUCinf: # subjects was 39

[23] - PK population

AUCinf: # subjects was 41

Statistical analyses

No statistical analyses for this end point

Secondary: Naloxone: Apparent clearance (CL/F)

| | |
|-----------------|-------------------------------------|
| End point title | Naloxone: Apparent clearance (CL/F) |
|-----------------|-------------------------------------|

End point description:

PK parameters were calculated from the concentration-time data using noncompartmental methods (Phoenix® WinNonlin®, version 6.3) and actual sampling times.

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

End point timeframe:

Predose and 5 minutes and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 (Day 2), 36, 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), and 144 hours (Day 7) post dose. Dosing days included Day 1, Day 22 and Day 43

| End point values | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat | |
|--------------------------------------|--|--|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 40 ^[24] | 39 ^[25] | 41 ^[26] | |
| Units: L/hour | | | | |
| arithmetic mean (standard deviation) | 18128.5 (± 6292.69) | 18900.8 (± 6242.62) | 15596.4 (± 5875.31) | |

Notes:

[24] - PK population

[25] - PK population

[26] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: Naloxone: Maximum observed plasma concentration (Cmax)

| | |
|-----------------|--|
| End point title | Naloxone: Maximum observed plasma concentration (Cmax) |
|-----------------|--|

End point description:

PK parameters were calculated from the concentration-time data using noncompartmental methods (Phoenix® WinNonlin®, version 6.3) and actual sampling times.

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

End point timeframe:

Predose and 5 minutes and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 (Day 2), 36, 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), and 144 hours (Day 7) post dose. Dosing days included Day 1, Day 22 and Day 43

| End point values | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat | |
|--------------------------------------|--|--|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 43 ^[27] | 43 ^[28] | 42 ^[29] | |
| Units: pg/mL | | | | |
| arithmetic mean (standard deviation) | 117.584 (± 59.6366) | 114.488 (± 54.9768) | 137.721 (± 131.51) | |

Notes:

[27] - PK population

[28] - PK population

[29] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: Naloxone: Time to maximum plasma concentration (Tmax)

| | |
|-----------------|---|
| End point title | Naloxone: Time to maximum plasma concentration (Tmax) |
|-----------------|---|

End point description:

PK parameters were calculated from the concentration-time data using noncompartmental methods (Phoenix® WinNonlin®, version 6.3) and actual sampling times.

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

End point timeframe:

Predose and 5 minutes and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 (Day 2), 36, 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), and 144 hours (Day 7) post dose. Dosing days included Day 1, Day 22 and Day 43

| End point values | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat | |
|-------------------------------|--|--|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 43 ^[30] | 43 ^[31] | 42 ^[32] | |
| Units: hours | | | | |
| median (full range (min-max)) | 0.5 (0.25 to 12) | 0.5 (0.08 to 10) | 0.875 (0.25 to 10) | |

Notes:

[30] - PK population

[31] - PK population

[32] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: Naloxone: Apparent volume of distribution (V_z/F)

| | |
|------------------------|---|
| End point title | Naloxone: Apparent volume of distribution (V _z /F) |
| End point description: | PK parameters were calculated from the concentration-time data using noncompartmental methods (Phoenix® WinNonlin®, version 6.3) and actual sampling times. |
| End point type | Secondary |

End point timeframe:

Predose and 5 minutes and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 (Day 2), 36, 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), and 144 hours (Day 7) post dose. Dosing days included Day 1, Day 22 and Day 43

| End point values | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat | |
|--------------------------------------|--|--|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 40 ^[33] | 39 ^[34] | 41 ^[35] | |
| Units: liters | | | | |
| arithmetic mean (standard deviation) | 281217.6 (± 148959.5) | 267134.2 (± 113638.7) | 200385 (± 79055.43) | |

Notes:

[33] - PK population

[34] - PK population

[35] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: Naloxone: Terminal phase half-life (T1/2)

| | |
|---|---|
| End point title | Naloxone: Terminal phase half-life (T1/2) |
| End point description: PK parameters were calculated from the concentration-time data using noncompartmental methods (Phoenix® WinNonlin®, version 6.3) and actual sampling times. | |
| End point type | Secondary |
| End point timeframe: Predose and 5 minutes and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 (Day 2), 36, 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), and 144 hours (Day 7) post dose. Dosing days included Day 1, Day 22 and Day 43 | |

| End point values | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat | |
|--------------------------------------|--|--|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 41 ^[36] | 39 ^[37] | 41 ^[38] | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | 10.941 (± 5.3226) | 9.625 (± 2.5029) | 9.061 (± 2.182) | |

Notes:

[36] - PK population

[37] - PK population

[38] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: Naloxone-3-Glucuronide: Area under the plasma concentration-time curve from time 0 to 72 hours post dose (AUC0-72), AUC0-96, AUCinf, and AUClast

| | |
|--|--|
| End point title | Naloxone-3-Glucuronide: Area under the plasma concentration-time curve from time 0 to 72 hours post dose (AUC0-72), AUC0-96, AUCinf, and AUClast |
| End point description: PK parameters were calculated from the concentration-time data using noncompartmental methods (Phoenix® WinNonlin®, version 6.3) and actual sampling times. | |
| End point type | Secondary |
| End point timeframe: Predose and 5 minutes and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 (Day 2), 36, 48 (Day 3), 72 hours (Day 4), post dose. Dosing days included Day 1, Day 22 and Day 43 | |

| End point values | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat | |
|--------------------------------------|--|--|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 43 ^[39] | 44 ^[40] | 43 ^[41] | |
| Units: hr*pg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| AUC0-72 (n=43, 44, 43) | 390626 (± 89104.2) | 388016 (± 884449.9) | 343377 (± 92323.5) | |
| AUC0-96 (n=43, 44, 43) | 391305 (± 89619) | 388920 (± 89401.2) | 343911 (± 92602) | |
| AUCinf (n=43, 43, 43) | 391536 (± 89784) | 384388 (± 84678.6) | 344084 (± 92695.7) | |
| AUClast (n=43, 44, 43) | 388867 (± 89699.2) | 386584 (± 89199.4) | 341692 (± 92391.1) | |

Notes:

[39] - PK population

[40] - PK population

AUCinf: # subjects was 43

[41] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: Naloxone-3-Glucuronide: Maximum observed plasma concentration (Cmax)

| | |
|-----------------|--|
| End point title | Naloxone-3-Glucuronide: Maximum observed plasma concentration (Cmax) |
|-----------------|--|

End point description:

PK parameters were calculated from the concentration-time data using noncompartmental methods (Phoenix® WinNonlin®, version 6.3) and actual sampling times.

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

End point timeframe:

Predose and 5 minutes and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 (Day 2), 36, 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), and 144 hours (Day 7) post dose. Dosing days included Day 1, Day 22 and Day 43

| End point values | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat | |
|--------------------------------------|--|--|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 43 ^[42] | 44 ^[43] | 43 ^[44] | |
| Units: pg/mL | | | | |
| arithmetic mean (standard deviation) | 189833 (± 56207.23) | 190464 (± 51991.93) | 77190.7 (± 41626.66) | |

Notes:

[42] - PK population

[43] - PK population

[44] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: Naloxone-3-Glucuronide: Time to maximum plasma concentration (Tmax)

| | |
|-----------------|---|
| End point title | Naloxone-3-Glucuronide: Time to maximum plasma concentration (Tmax) |
|-----------------|---|

End point description:

PK parameters were calculated from the concentration-time data using noncompartmental methods (Phoenix® WinNonlin®, version 6.3) and actual sampling times.

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

End point timeframe:

Predose and 5 minutes and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 (Day 2), 36, 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), and 144 hours (Day 7) post dose. Dosing days included Day 1, Day 22 and Day 43

| End point values | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat | |
|-------------------------------|--|--|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 43 ^[45] | 44 ^[46] | 43 ^[47] | |
| Units: hours | | | | |
| median (full range (min-max)) | 0.5 (0.25 to 2) | 0.5 (0.25 to 3) | 1.5 (0.25 to 4) | |

Notes:

[45] - PK population

[46] - PK population

[47] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: Naloxone-3-Glucuronide: Terminal phase half-life (T1/2)

| | |
|-----------------|---|
| End point title | Naloxone-3-Glucuronide: Terminal phase half-life (T1/2) |
|-----------------|---|

End point description:

PK parameters were calculated from the concentration-time data using noncompartmental methods (Phoenix® WinNonlin®, version 6.3) and actual sampling times.

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

End point timeframe:

Predose and 5 minutes and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 (Day 2), 36, 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), and 144 hours (Day 7) post dose. Dosing days included Day 1, Day 22 and Day 43

| End point values | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat | |
|--------------------------------------|--|--|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 43 ^[48] | 43 ^[49] | 43 ^[50] | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | 8.497 (± 2.5606) | 8.255 (± 2.9189) | 8.339 (± 2.5873) | |

Notes:

[48] - PK population

[49] - PK population

[50] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: Buprenorphine Hemiadipate: Area under the plasma concentration-time curve from time 0 to 72 hours post dose (AUC0-72), AUC0-96, AUCinf, and AUClast

| | |
|-----------------|---|
| End point title | Buprenorphine Hemiadipate: Area under the plasma concentration-time curve from time 0 to 72 hours post dose (AUC0-72), AUC0-96, AUCinf, and AUClast |
|-----------------|---|

End point description:

PK parameters were calculated from the concentration-time data using noncompartmental methods (Phoenix® WinNonlin®, version 6.3) and actual sampling times.

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

End point timeframe:

Predose and 5 minutes and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 (Day 2), 36, 48 (Day 3), 72 hours (Day 4), post dose. Dosing days included Day 1, Day 22 and Day 43

| End point values | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat | |
|--------------------------------------|--|--|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 37 ^[51] | 36 ^[52] | 28 ^[53] | |
| Units: hr*ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| AUC0-72 (n=37, 36, 28) | 1.006 (± 0.6769) | 1.036 (± 0.5688) | 1.671 (± 0.8329) | |
| AUC0-96 (n=37, 36, 28) | 1.006 (± 0.6769) | 1.036 (± 0.5689) | 1.672 (± 0.8329) | |
| AUCinf (n=33, 30, 19) | 1.036 (± 0.7017) | 1.036 (± 0.5832) | 1.8 (± 0.8657) | |
| AUClast (n=43, 44, 43) | 0.863 (± 0.6558) | 0.832 (± 0.5681) | 1.327 (± 0.7492) | |

Notes:

[51] - PK population

AUCinf: # subjects was 33

AUClast: # subjects was 43

[52] - PK population

AUCinf: # subjects was 30

AUClast: # subjects was 44

[53] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: Buprenorphine Hemiadipate: Apparent clearance (CL/F)

| | |
|-----------------|--|
| End point title | Buprenorphine Hemiadipate: Apparent clearance (CL/F) |
|-----------------|--|

End point description:

PK parameters were calculated from the concentration-time data using noncompartmental methods (Phoenix® WinNonlin®, version 6.3) and actual sampling times.

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

End point timeframe:

Predose and 5 minutes and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 (Day 2), 36, 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), and 144 hours (Day 7) post dose. Dosing days included Day 1, Day 22 and Day 43

| End point values | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat | |
|--------------------------------------|--|--|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 33 ^[54] | 30 ^[55] | 19 ^[56] | |
| Units: L/hour | | | | |
| arithmetic mean (standard deviation) | 12696.7 (± 7618.39) | 12110.1 (± 6588.64) | 6282.36 (± 2571.67) | |

Notes:

[54] - PK population

[55] - PK population

[56] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: Buprenorphine Hemiadipate: Maximum observed plasma concentration (Cmax)

| | |
|-----------------|---|
| End point title | Buprenorphine Hemiadipate: Maximum observed plasma concentration (Cmax) |
|-----------------|---|

End point description:

PK parameters were calculated from the concentration-time data using noncompartmental methods (Phoenix® WinNonlin®, version 6.3) and actual sampling times.

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

End point timeframe:

Predose and 5 minutes and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 (Day 2), 36, 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), and 144 hours (Day 7) post dose. Dosing days included Day 1, Day 22 and Day 43

| End point values | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat | |
|--------------------------------------|--|--|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 43 ^[57] | 44 ^[58] | 43 ^[59] | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 1.102 (± 0.8978) | 0.978 (± 0.8173) | 0.842 (± 0.7135) | |

Notes:

[57] - PK population

[58] - PK population

[59] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: Buprenorphine Hemiadipate: Time to maximum plasma concentration (Tmax)

| | |
|-----------------|--|
| End point title | Buprenorphine Hemiadipate: Time to maximum plasma concentration (Tmax) |
|-----------------|--|

End point description:

PK parameters were calculated from the concentration-time data using noncompartmental methods (Phoenix® WinNonlin®, version 6.3) and actual sampling times.

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

End point timeframe:

Predose and 5 minutes and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 (Day 2), 36, 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), and 144 hours (Day 7) post dose. Dosing days included Day 1, Day 22 and Day 43

| End point values | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat | |
|-------------------------------|--|--|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 43 ^[60] | 44 ^[61] | 43 ^[62] | |
| Units: hours | | | | |
| median (full range (min-max)) | 0.5 (0.25 to 4) | 0.5 (0.25 to 3) | 1.25 (0.25 to 8) | |

Notes:

[60] - PK population

[61] - PK population

[62] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: Buprenorphine Hemiadipate: Apparent volume of distribution (Vz/F)

| | |
|---|--|
| End point title | Buprenorphine Hemiadipate: Apparent volume of distribution (V _z /F) |
| End point description: PK parameters were calculated from the concentration-time data using noncompartmental methods (Phoenix® WinNonlin®, version 6.3) and actual sampling times. | |
| End point type | Secondary |
| End point timeframe: Predose and 5 minutes and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 (Day 2), 36, 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), and 144 hours (Day 7) post dose. Dosing days included Day 1, Day 22 and Day 43 | |

| End point values | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat | |
|--------------------------------------|----------------------------------|----------------------------------|-----------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 33 ^[63] | 30 ^[64] | 19 ^[65] | |
| Units: liters | | | | |
| arithmetic mean (standard deviation) | 7166.63 (± 4169.24) | 7587.57 (± 5268.287) | 8468.05 (± 5464.365) | |

Notes:

[63] - PK population

[64] - PK population

[65] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: Buprenorphine Hemiadipate: Terminal phase half-life (T_{1/2})

| | |
|---|---|
| End point title | Buprenorphine Hemiadipate: Terminal phase half-life (T _{1/2}) |
| End point description: PK parameters were calculated from the concentration-time data using noncompartmental methods (Phoenix® WinNonlin®, version 6.3) and actual sampling times. | |
| End point type | Secondary |
| End point timeframe: Predose and 5 minutes and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 (Day 2), 36, 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), and 144 hours (Day 7) post dose. Dosing days included Day 1, Day 22 and Day 43 | |

| End point values | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat | |
|--------------------------------------|----------------------------------|----------------------------------|-----------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 33 ^[66] | 31 ^[67] | 22 ^[68] | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | 0.417 (± 0.2047) | 0.473 (± 0.2307) | 1.174 (± 0.994) | |

Notes:

[66] - PK population

[67] - PK population

[68] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: Norbuprenorphine: Area under the plasma concentration-time curve from time 0 to 72 hours post dose (AUC0-72), AUC0-96, AUCinf, and AUClast

| | |
|-----------------|--|
| End point title | Norbuprenorphine: Area under the plasma concentration-time curve from time 0 to 72 hours post dose (AUC0-72), AUC0-96, AUCinf, and AUClast |
|-----------------|--|

End point description:

PK parameters were calculated from the concentration-time data using noncompartmental methods (Phoenix® WinNonlin®, version 6.3) and actual sampling times.

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

End point timeframe:

Predose and 5 minutes and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 (Day 2), 36, 48 (Day 3), 72 hours (Day 4), post dose. Dosing days included Day 1, Day 22 and Day 43

| End point values | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat | |
|--------------------------------------|--|--|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 43 ^[69] | 43 ^[70] | 43 ^[71] | |
| Units: hr*ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| AUC0-72 (n=43, 43, 43) | 28.97 (± 9.136) | 29.79 (± 10.5179) | 32.819 (± 12.7461) | |
| AUC0-96 (n=43, 43, 43) | 33.794 (± 10.4778) | 34.942 (± 12.2799) | 38.743 (± 15.0137) | |
| AUCinf (n=38, 37, 39) | 43.891 (± 14.5846) | 46.056 (± 16.673) | 51.029 (± 21.2304) | |
| AUClast (n=43, 43, 43) | 38.673 (± 12.949) | 39.932 (± 15.1644) | 44.967 (± 18.387) | |

Notes:

[69] - PK population

AUCinf: # subjects was 38

[70] - PK population

AUCinf: # subjects was 37

[71] - PK population

AUCinf: # subjects was 39

Statistical analyses

No statistical analyses for this end point

Secondary: Norbuprenorphine: Maximum observed plasma concentration (Cmax)

| | |
|-----------------|--|
| End point title | Norbuprenorphine: Maximum observed plasma concentration (Cmax) |
|-----------------|--|

End point description:

PK parameters were calculated from the concentration-time data using noncompartmental methods (Phoenix® WinNonlin®, version 6.3) and actual sampling times.

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

End point timeframe:

Predose and 5 minutes and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 (Day 2), 36, 48 (Day 3), 72 hours (Day 4), post dose. Dosing days included Day 1, Day 22 and Day 43

| End point values | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat | |
|--------------------------------------|--|--|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 43 ^[72] | 43 ^[73] | 43 ^[74] | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 1.287 (± 0.5964) | 1.192 (± 0.578) | 1.011 (± 0.4969) | |

Notes:

[72] - PK population

[73] - PK population

[74] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: Norbuprenorphine: Time to maximum plasma concentration (Tmax)

| | |
|-----------------|---|
| End point title | Norbuprenorphine: Time to maximum plasma concentration (Tmax) |
|-----------------|---|

End point description:

PK parameters were calculated from the concentration-time data using noncompartmental methods (Phoenix® WinNonlin®, version 6.3) and actual sampling times.

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

End point timeframe:

Predose and 5 minutes and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 (Day 2), 36, 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), and 144 hours (Day 7) post dose. Dosing days included Day 1, Day 22 and Day 43

| End point values | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat | |
|-------------------------------|--|--|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 43 ^[75] | 43 ^[76] | 43 ^[77] | |
| Units: hours | | | | |
| median (full range (min-max)) | 1 (0.5 to 8) | 1.25 (0.5 to 6) | 3 (0.75 to 12) | |

Notes:

[75] - PK population

[76] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: Norbuprenorphine: Terminal phase half-life (T1/2)

| | |
|---|---|
| End point title | Norbuprenorphine: Terminal phase half-life (T1/2) |
| End point description: | |
| PK parameters were calculated from the concentration-time data using noncompartmental methods (Phoenix® WinNonlin®, version 6.3) and actual sampling times. | |
| End point type | Secondary |
| End point timeframe: | |
| Predose and 5 minutes and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 (Day 2), 36, 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), and 144 hours (Day 7) post dose. Dosing days included Day 1, Day 22 and Day 43 | |

| End point values | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat | |
|--------------------------------------|--|--|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 43 ^[78] | 43 ^[79] | 43 ^[80] | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | 44.677 (± 14.9785) | 43.902 (± 11.8023) | 44.975 (± 17.4439) | |

Notes:

[78] - PK population

[79] - PK population

[80] - PK population

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects with Treatment-Emergent Adverse Events (TEAEs)

| | |
|---|---|
| End point title | Subjects with Treatment-Emergent Adverse Events (TEAEs) |
| End point description: | |
| Treatment-emergent AEs (TEAEs) were defined as AEs (any untoward medical occurrence) that either commenced following initiation of randomised study treatment or were present prior to randomised study treatment but increased in frequency or severity following initiation of randomised study treatment. TEAEs that occurred following administration of study treatment in Period 1 but before administration of study treatment in Period 2 were attributed to the treatment administered in Period 1 (and the same for Period 2). If the time was missing for an AE on Day 1 of any period, then the AE was attributed to the treatment administered on that day. The investigator assessed whether a TEAE was likely related to study treatment, and also the severity rating for the TEAE (mild, moderate or severe). | |
| End point type | Secondary |

End point timeframe:

Day 1 to Week 10

| End point values | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat | |
|--------------------------------------|--|--|---|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 47 ^[81] | 47 ^[82] | 44 ^[83] | |
| Units: subjects | | | | |
| At least one TEAE | 35 | 36 | 25 | |
| TEAE considered related to treatment | 26 | 20 | 15 | |
| Severe TEAE | 0 | 0 | 0 | |
| TEAE leading to withdrawal | 4 | 2 | 0 | |

Notes:

[81] - Safety population: All subjects who received at least 1 dose of study treatment

[82] - Safety population: All subjects who received at least 1 dose of study treatment

[83] - Safety population: All subjects who received at least 1 dose of study treatment

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Week 10

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------------------|
| Reporting group title | RBP-6300 Formulation A - Fasting |
|-----------------------|----------------------------------|

Reporting group description:

RBP-6300 Formulation A (10 mg buprenorphine hemiadipate HCl/10 mg naloxone HCl dihydrate) administered as an oral tablet after an overnight fast of at least 10 hours.

| | |
|-----------------------|----------------------------------|
| Reporting group title | RBP-6300 Formulation B - Fasting |
|-----------------------|----------------------------------|

Reporting group description:

RBP-6300 Formulation B (10 mg buprenorphine hemiadipate HCl/10 mg naloxone HCl dihydrate) administered as an oral tablet after an overnight fast of at least 10 hours.

| | |
|-----------------------|-----------------------------------|
| Reporting group title | RBP-6300 Formulation A - High Fat |
|-----------------------|-----------------------------------|

Reporting group description:

RBP-6300 Formulation A administered as an oral tablet within 30 minutes of starting and completing a high-fat breakfast following an overnight fast of at least 10 hours.

| Serious adverse events | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat |
|---|--|--|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 47 (0.00%) | 0 / 44 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

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

| Non-serious adverse events | RBP-6300 Formulation A - Fasting | RBP-6300 Formulation B - Fasting | RBP-6300 Formulation A - High Fat |
|---|--|--|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 35 / 47 (74.47%) | 36 / 47 (76.60%) | 25 / 44 (56.82%) |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 13 / 47 (27.66%) | 12 / 47 (25.53%) | 8 / 44 (18.18%) |
| occurrences (all) | 13 | 15 | 10 |
| Catheter site pain | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 47 (2.13%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 1 | 1 |
| Feeling hot | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 1 / 47 (2.13%) | 1 / 44 (2.27%) |
| occurrences (all) | 1 | 2 | 1 |
| Feeling cold | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 47 (2.13%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Feeling of relaxation | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 47 (2.13%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gravitational oedema | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 47 (2.13%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hunger | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 47 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infusion site rash | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 47 (2.13%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 47 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 47 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 1 | 0 | 1 |
| Cough | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 47 (2.13%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 47 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Psychiatric disorders | | | |

| | | | |
|--|------------------------|----------------------|----------------------|
| Insomnia subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 47 (2.13%) 1 | 0 / 44 (0.00%) 0 |
| Nightmare subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 47 (2.13%) 1 | 0 / 44 (0.00%) 0 |
| Injury, poisoning and procedural complications Laceration subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 0 / 47 (0.00%) 0 | 1 / 44 (2.27%) 1 |
| Periorbital contusion subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 0 / 47 (0.00%) 0 | 1 / 44 (2.27%) 1 |
| Cardiac disorders Palpitations subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 47 (2.13%) 1 | 0 / 44 (0.00%) 0 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 12 / 47 (25.53%) 12 | 6 / 47 (12.77%) 6 | 9 / 44 (20.45%) 9 |
| Somnolence subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 3 / 47 (6.38%) 4 | 4 / 44 (9.09%) 5 |
| Loss of consciousness subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 0 / 47 (0.00%) 0 | 1 / 44 (2.27%) 1 |
| Disturbance in attention subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 0 / 47 (0.00%) 0 | 0 / 44 (0.00%) 0 |
| Dizziness subjects affected / exposed occurrences (all) | 4 / 47 (8.51%) 5 | 4 / 47 (8.51%) 5 | 0 / 44 (0.00%) 0 |
| Dysgeusia subjects affected / exposed occurrences (all) | 2 / 47 (4.26%) 2 | 0 / 47 (0.00%) 0 | 0 / 44 (0.00%) 0 |

| | | | |
|--|----------------------|------------------------|---------------------|
| Lethargy subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 0 | 0 / 47 (0.00%) 0 | 0 / 44 (0.00%) 0 |
| Nervousness subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 0 / 47 (0.00%) 0 | 0 / 44 (0.00%) 0 |
| Ear and labyrinth disorders Hypoacusis subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 0 / 47 (0.00%) 0 | 0 / 44 (0.00%) 0 |
| Eye disorders Blepharospasm subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 47 (2.13%) 1 | 0 / 44 (0.00%) 0 |
| Conjunctival haemorrhage subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 0 / 47 (0.00%) 0 | 0 / 44 (0.00%) 0 |
| Dry eye subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 47 (2.13%) 1 | 0 / 44 (0.00%) 0 |
| Ocular hyperaemia subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 0 / 47 (0.00%) 0 | 0 / 44 (0.00%) 0 |
| Photophobia subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 0 / 47 (0.00%) 0 | 0 / 44 (0.00%) 0 |
| Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) | 3 / 47 (6.38%) 3 | 1 / 47 (2.13%) 2 | 3 / 44 (6.82%) 3 |
| Nausea subjects affected / exposed occurrences (all) | 9 / 47 (19.15%) 9 | 10 / 47 (21.28%) 11 | 3 / 44 (6.82%) 3 |
| Abdominal distension subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 2 / 47 (4.26%) 2 | 1 / 44 (2.27%) 1 |
| Abdominal pain upper | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 2 / 47 (4.26%) | 5 / 47 (10.64%) | 1 / 44 (2.27%) |
| occurrences (all) | 2 | 5 | 1 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 47 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 0 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 4 / 47 (8.51%) | 4 / 47 (8.51%) | 1 / 44 (2.27%) |
| occurrences (all) | 4 | 4 | 1 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 2 / 47 (4.26%) | 0 / 44 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | 2 / 47 (4.26%) | 0 / 44 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 47 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Eczema | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 47 (2.13%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Renal and urinary disorders | | | |
| Bladder disorder | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 47 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 0 | 1 |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 47 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 0 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 47 (2.13%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 1 | 1 |
| Tendon pain | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 0 / 47 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 0 | 1 |
| Muscle twitching | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 47 (2.13%) 1 | 0 / 44 (0.00%) 0 |
| Infections and infestations Vulvovaginal candidiasis subjects affected / exposed occurrences (all) | 0 / 47 (0.00%) 0 | 1 / 47 (2.13%) 1 | 0 / 44 (0.00%) 0 |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | 0 / 47 (0.00%) 0 | 2 / 44 (4.55%) 2 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 28 January 2013 | The first amendment, dated 28 January 2013, was approved prior to the initiation of study conduct at Celerion. The purpose of the amendment was to change the PI for the study. |
| 15 August 2013 | <p>The second amendment, dated 15 August 2013, was issued to change the clinical facility and PI, change the Medical Monitor, move urine PK from secondary objectives to exploratory objectives, add metabolic profiling as an exploratory objective, clarify urine aliquotting procedures, clarify collection of temperature, define the number of completers required, and add details regarding total blood volume collected. Changes to the procedures for the fed conditions and the volume of water provided at study treatment administration were updated to match the appropriate guidelines. The following changes were also made to make the study procedures more consistent with the other trials in the clinical program:</p> <p>Naltrexone dosing regimen was changed. Inclusion/Exclusion criteria were changed. Telemetry and ECGs were added. Clinical laboratory tests were changed.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported