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 (Formualtion A) 10 mg as compared to RBP 6300 (Formualtion 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-naive, healthy subjects.
Naltrexone 100 mg was given at 13 hours [± 1 hour] and at 2 hours [± 15 minutes] predose. It was also given 50 mg at 12 hours [± 1 hour] and 24 hours [± 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 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.
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

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

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

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)

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 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	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 (Cmax)

End point title	Buprenorphine: 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. 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 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 ere 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 ere 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 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	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 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.
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 (Vz/F)

End point title	Naloxone: 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.

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

AUCinf: # subjects was 19
AUClast: # subjects was 43

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 (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.

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 (T1/2)

End point title	Buprenorphine Hemiadipate: 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	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

[77] - 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	0 / 47 (0.00%)	1 / 47 (2.13%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Nightmare			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Laceration			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Periorbital contusion			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 47 (25.53%)	6 / 47 (12.77%)	9 / 44 (20.45%)
occurrences (all)	12	6	9
Somnolence			
subjects affected / exposed	1 / 47 (2.13%)	3 / 47 (6.38%)	4 / 44 (9.09%)
occurrences (all)	1	4	5
Loss of consciousness			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Disturbance in attention			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	4 / 47 (8.51%)	4 / 47 (8.51%)	0 / 44 (0.00%)
occurrences (all)	5	5	0
Dysgeusia			
subjects affected / exposed	2 / 47 (4.26%)	0 / 47 (0.00%)	0 / 44 (0.00%)
occurrences (all)	2	0	0

Lethargy			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Nervousness			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Blepharospasm			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Conjunctival haemorrhage			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Dry eye			
subjects affected / exposed	0 / 47 (0.00%)	1 / 47 (2.13%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Ocular hyperaemia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Photophobia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 47 (6.38%)	1 / 47 (2.13%)	3 / 44 (6.82%)
occurrences (all)	3	2	3
Nausea			
subjects affected / exposed	9 / 47 (19.15%)	10 / 47 (21.28%)	3 / 44 (6.82%)
occurrences (all)	9	11	3
Abdominal distension			
subjects affected / exposed	1 / 47 (2.13%)	2 / 47 (4.26%)	1 / 44 (2.27%)
occurrences (all)	1	2	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	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: Naltrexone dosing regimen was changed. Inclusion/Exclusion criteria were changed. Telemetry and ECGs were added. Clinical laboratory tests were changed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported