Clinical trial results:
A randomised, interventional, double blind, crossover, controlled study to assess the effect of the administration of paracetamol on tramadol adverse events.

Summary

EudraCT number	2017-002668-42
Trial protocol	BG
Global end of trial date	14 February 2018

Results information

Result version number	v1 (current)
This version publication date	26 October 2018
First version publication date	26 October 2018

Trial information

Trial identification

Sponsor protocol code	TRA-IV-17-1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Laboratoires SMB S.A.
Sponsor organisation address	26-28, rue de la Pastorale, Brussels, Belgium, 1080
Public contact	Clinical Department, Laboratoires SMB S.A., 0032 24114828, Dpt_Clinique@smb.be
Scientific contact	Clinical Department, Laboratoires SMB S.A., 0032 24114828, Dpt_Clinique@smb.be

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	15 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 February 2018
Global end of trial reached?	Yes
Global end of trial date	14 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effects of paracetamol on the tramadol safety profile.

Protection of trial subjects:

For this study, no specific measures were put in place to protect trial subjects. The study treatments (Tramadol & Paracetamol) were two products marketed by the Laboratoires SMB since many years and then were well known by most of the participating subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 November 2017
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	Bulgaria: 150
Worldwide total number of subjects	150
EEA total number of subjects	150

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)	150
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in one center in Bulgaria. The subject recruitment was adequate to meet the target enrolment goal of 150 subjects. After the screening visit, the subjects were randomized in one of the two sequences of treatment and stayed in the study for a minimum of 11 days.

Pre-assignment

Screening details:

-Obtain signed ICF
- Obtain demographic data
-Perform a medical history and a physical examination
-Take vital signs
-Review prior/concomitant médications
_Perform laboratory assessments: haematology, chemistry, and pregnancy test
-Review inclusion/exclusion criteria

Period 1

Period 1 title	Cross over phase (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	No
Arm title	Tramadol + Placebo

Arm description:

The subjects received tramadol + placebo during two consecutive days.

Arm type	Active comparator
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablet for oral use containing only the excipients of the active substance (Paracetamol). One tablet was taken three times per day (T0, T6, T12) on day 1 and 2 of the period.

Investigational medicinal product name	Tramadol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release capsule
Routes of administration	Oral use

Dosage and administration details:

Tramium (Tramadol) prolonged release capsule for oral use containing 200 mg of tramadol chlorhydrate. One capsule was taken once a day on day 1 and 2 of the period.

Arm title	Tramadol + Paracetamol

Arm description:

The subjects received tramadol + paracetamol during two consecutive days.

Arm type	Experimental

Investigational medicinal product name	Paracetamol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Paracetamol (Algostase Mono) tablet for oral use containing 500 mg of paracetamol. One tablet was taken three times per day (T0, T6, T12) on day 1 and 2 of the period.

Investigational medicinal product name	Tramadol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Prolonged-release capsule
Routes of administration	Oral use

Dosage and administration details:

Tramium (Tramadol) prolonged release capsule for oral use containing 200 mg of tramadol chlorhydrate. One capsule was taken once a day on day 1 and 2 of the period.

Number of subjects in period 1	Tramadol + Placebo	Tramadol + Paracetamol
Started	149	150
Completed	149	149
Not completed	0	1
Consent withdrawn by subject	-	1

Baseline characteristics

Reporting groups

Reporting group title	Cross over phase

Reporting group description: -

Reporting group values	Cross over phase	Total	
Number of subjects	150	150	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	150	150	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	39.91		
standard deviation	± 12.06	-	
Gender categorical Units: Subjects			
Female	86	86	
Male	64	64	

End points

End points reporting groups	
Reporting group title	Tramadol + Placebo
Reporting group description:	
The subjects received tramadol + placebo during two consecutive days.	
Reporting group title	Tramadol + Paracetamol
Reporting group description:	
The subjects received tramadol + paracetamol during two consecutive days.	

Primary: Adverse Events	
End point title	Adverse Events
End point description:	
End point type	Primary
End point timeframe:	
Adverse event reporting started from signature of the subject informed consent form and ended by a phone call 7 days (+-1 day) after the last visit at site.	

End point values	Tramadol + Placebo	Tramadol + Paracetamol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	150		
Units: number	116	85		

Statistical analyses

Statistical analysis title	Descriptive statistics
Comparison groups	Tramadol + Placebo v Tramadol + Paracetamol
Number of subjects included in analysis	299
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.05
Method	Chi-squared

Adverse events

Adverse events information	
Timeframe for reporting adverse events: AE reporting started from signature of the subject informed consent form and ended by a phone call 7 days (+- 1 day) after the last day at site.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Tramadol + Paracetamol
Reporting group description: -	
Reporting group title	Tramadol + Placebo
Reporting group description: -	

Serious adverse events	Tramadol + Paracetamol	Tramadol + Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 150 (0.00%)	0 / 149 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Tramadol + Paracetamol	Tramadol + Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 150 (30.00%)	56 / 149 (37.58%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	20 / 150 (13.33%)	18 / 149 (12.08%)	
occurrences (all)	22	20	
Headache			
subjects affected / exposed	10 / 150 (6.67%)	12 / 149 (8.05%)	
occurrences (all)	11	13	
Somnolence			
subjects affected / exposed	9 / 150 (6.00%)	8 / 149 (5.37%)	
occurrences (all)	10	9	
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	8 / 150 (5.33%)	7 / 149 (4.70%)	
occurrences (all)	10	7	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	8 / 150 (5.33%)	8 / 149 (5.37%)	
occurrences (all)	8	8	
Vomiting			
subjects affected / exposed	12 / 150 (8.00%)	29 / 149 (19.46%)	
occurrences (all)	17	53	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported