



## 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:

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**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:

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**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:

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**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:

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**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 medications
- \_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                 |
| <b>Arm title</b>             | 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.

|                  |                        |
|------------------|------------------------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 1</b> | 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<br>(gestational age < 37 wks) | 0                | 0     |  |
| Newborns (0-27 days)                                  | 0                | 0     |  |
| Infants and toddlers (28 days-23<br>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:<br>The subjects received tramadol + placebo during two consecutive days.     |                        |
| Reporting group title                                                                                     | Tramadol + Paracetamol |
| Reporting group description:<br>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:<br>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<br>subjects affected / exposed<br>occurrences (all)  | 8 / 150 (5.33%)<br>10  | 7 / 149 (4.70%)<br>7    |  |
| Gastrointestinal disorders                                   |                        |                         |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)   | 8 / 150 (5.33%)<br>8   | 8 / 149 (5.37%)<br>8    |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all) | 12 / 150 (8.00%)<br>17 | 29 / 149 (19.46%)<br>53 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported