



## Clinical trial results:

### Evaluation of the relationship between effervescent acetaminophen and blood pressure. A clinical trial.

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2010-023485-53 |
| Trial protocol           | ES             |
| Global end of trial date | 29 March 2016  |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 29 June 2022 |
| First version publication date | 29 June 2022 |

#### Trial information

##### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | IJG-PAR-2010 |
|-----------------------|--------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02514538 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | IDIAP Jordi Gol   |
| Sponsor organisation address | Gran Via de les Corts Catalanes, 587, Barcelona, Spain, 08007   |
| Public contact               | Ana Garcia-Sangenis, IDIAP Jordi Gol - UEM, +34 934824644, <a href="mailto:agarcia@idiapjgol.org">agarcia@idiapjgol.org</a> |
| Scientific contact           | Ana Garcia-Sangenis, IDIAP Jordi Gol - UEM, +34 934824644, <a href="mailto:agarcia@idiapjgol.org">agarcia@idiapjgol.org</a> |

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                       | 29 March 2016 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 29 March 2016 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 29 March 2016 |
| Was the trial ended prematurely?                     | No            |

Notes:

---

**General information about the trial**

Main objective of the trial:

To evaluate the effect on blood pressure of effervescent paracetamol compared to non-effervescent paracetamol, in hypertensive patients.

Protection of trial subjects:

Routine care.

As recommended for second-line analgesic treatment, 50-mg tramadol every 8 h was permitted if pain persisted at a level more than 3 on the VAS.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 09 February 2012 |
| 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 | Spain: 49 |
| Worldwide total number of subjects   | 49        |
| EEA total number of subjects         | 49        |

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)                      | 12 |
| From 65 to 84 years                       | 37 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Recruitment period: February 2012 - June 2014 (Catalonia, Spain).

Primary Health Care Sites

Multicenter, randomized, controlled, cross-over, open, phase IV clinical trial.

### Pre-assignment

Screening details:

Wash out period of 3-15 days before first treatment period. During the washout periods, tramadol was the only analgesic allowed.

Patients included in the study were older than 18 years, with hypertension, chronic osteoarticular pain, and usual need of analgesic treatment.

59 patients were screened for eligibility, 10 were not randomized.

### Pre-assignment period milestones

|                              |                   |
|------------------------------|-------------------|
| Number of subjects started   | 59 <sup>[1]</sup> |
| Number of subjects completed | 49                |

### Pre-assignment subject non-completion reasons

|                            |   |
|----------------------------|---|
| Reason: Number of subjects | not give informed consent: 5              |
| Reason: Number of subjects | non compliance with inclusion criteria: 5 |

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 10 patients are screened but not enrolled

### Period 1

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

### Arms

|                              |                                      |
|------------------------------|--------------------------------------|
| Are arms mutually exclusive? | Yes                                  |
| <b>Arm title</b>             | AB - Effervescent - Non effervescent |

Arm description:

Wash out period (3-15 days) / Effervescent paracetamol 3 weeks/wash out period (3-15 days) / non-effervescent paracetamol 3 weeks

|  |                               |
|--|-------------------------------|
| Arm type                               | Experimental                  |
| Investigational medicinal product name | Paracetamol                   |
| Investigational medicinal product code |                               |
| Other name                             |                               |
| Pharmaceutical forms                   | Oral powder in sachet, Tablet |
| Routes of administration               | Oral use                      |

Dosage and administration details:

period A: 1g effervescent paracetamol (oral powder in sachet) every 8h during 3 weeks

period B: 1g non-effervescent paracetamol (tablet) every 8h during 3 weeks

|                  |                                      |
|------------------|--------------------------------------|
| <b>Arm title</b> | BA - Non effervescent - effervescent |
|------------------|--------------------------------------|

Arm description:

Wash out period (3-15 days) / Non- Effervescent paracetamol 3 weeks/wash out period (3-15 days) / Effervescent paracetamol 3 weeks

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |                               |
|--|-------------------------------|
| Investigational medicinal product name | Paracetamol                   |
| Investigational medicinal product code |                               |
| Other name                             |                               |
| Pharmaceutical forms                   | Oral powder in sachet, Tablet |
| Routes of administration               | Oral use                      |

Dosage and administration details:

Paracetamol (tablet) 1 gram every 8 hours during 3 weeks. Paracetamol (oral effervescent powder) 1 gram every 8 hours during 3 weeks

| Number of subjects in period 1 | AB - Effervescent -<br>Non effervescent | BA - Non<br>effervescent -<br>effervescent |
|--------------------------------|---|--|
|                                |   |  |
| Started                        | 24                                      | 25   |
| Completed                      | 14                                      | 21   |
| Not completed                  | 10                                      | 4  |
| Consent withdrawn by subject   | 1                                       | -  |
| Adverse event, non-fatal       | 1                                       | -  |
| Lost to follow-up              | 1                                       | -  |
| Protocol deviation             | 7                                       | 4  |

## Baseline characteristics

### Reporting groups

|  |                                      |
|--|--------------------------------------|
| Reporting group title  | AB - Effervescent - Non effervescent |
| Reporting group description:<br>Wash out period (3-15 days) / Effervescent paracetamol 3 weeks/wash out period (3-15 days) / non-effervescent paracetamol 3 weeks  |                                      |
| Reporting group title  | BA - Non effervescent - effervescent |
| Reporting group description:<br>Wash out period (3-15 days) / Non- Effervescent paracetamol 3 weeks/wash out period (3-15 days) / Effervescent paracetamol 3 weeks |                                      |

| Reporting group values                             | AB - Effervescent - Non effervescent | BA - Non effervescent - effervescent | Total |
|--|--------------------------------------|--------------------------------------|-------|
| Number of subjects                                 | 24                                   | 25                                   | 49    |
| Age categorical<br>Units: Subjects                 |                                      |                                      |       |
| In utero   |                                      |                                      | 0     |
| Preterm newborn infants (gestational age < 37 wks) |                                      |                                      | 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)                               |                                      |                                      | 0     |
| From 65-84 years                                   |                                      |                                      | 0     |
| 85 years and over                                  |                                      |                                      | 0     |
| Age continuous<br>Units: years                     |                                      |                                      |       |
| arithmetic mean                                    | 66.8                                 | 67.1                                 |       |
| standard deviation                                 | ± 9.6                                | ± 8.3                                | -     |
| Gender categorical<br>Units: Subjects              |                                      |                                      |       |
| Female   | 18                                   | 20                                   | 38    |
| Male   | 6                                    | 5                                    | 11    |

## End points

### End points reporting groups

|  |                                      |
|--|--------------------------------------|
| Reporting group title  | AB - Effervescent - Non effervescent |
| Reporting group description:<br>Wash out period (3-15 days) / Effervescent paracetamol 3 weeks/wash out period (3-15 days) / non-effervescent paracetamol 3 weeks  |                                      |
| Reporting group title  | BA - Non effervescent - effervescent |
| Reporting group description:<br>Wash out period (3-15 days) / Non- Effervescent paracetamol 3 weeks/wash out period (3-15 days) / Effervescent paracetamol 3 weeks |                                      |
| Subject analysis set title   | Effervescent paracetamol             |
| Subject analysis set type  | Full analysis                        |
| Subject analysis set description:<br>All subjects that have initiated effervescent paracetamol treatment.  |                                      |
| Subject analysis set title   | Non-Effervescent paracetamol         |
| Subject analysis set type  | Full analysis                        |
| Subject analysis set description:<br>All patients that have initiated non effervescent paracetamol treatment   |                                      |

### Primary: Increase in 24h Systolic Blood Pressure (SBP)

|  |   |
|--|---|
| End point title  | Increase in 24h Systolic Blood Pressure (SBP) |
| End point description:<br>Crossover study.<br>Difference in 24h SBP when 3 weeks treatment of non effervescent paracetamol vs 3 weeks treatment of effervescent paracetamol.<br>In the ITT analysis, treatment with effervescent paracetamol was associated with an increase of 3.59mmHg (95% CI 1.39–5.79; P=0.003) in 24-h SBP, and noneffervescent paracetamol with a 0.33-mmHg reduction (95% CI -1.78 to -1.13; P=0.886); the difference in 24-h SBP between the two treatments was 3.99mmHg (95% CI 1.35–6.63; P=0.004), higher in the effervescent paracetamol treatment periods.<br>Similarly, the per-protocol analysis showed an increase of 4.57mmHg in 24-h SBP (95% CI 2.01–7.13) under effervescent paracetamol treatment and a reduction of 0.21mmHg (95% CI -2.12 to -1.71; P=0.009) at the end of noneffervescent paracetamol treatment.<br>The difference in 24-h SBP between the two groups was 5.04mmHg (95% CI 1.80–8.28; P=0.004). |   |
| End point type   | Primary                                       |
| End point timeframe:<br>3 weeks  |   |

| End point values                 | Effervescent paracetamol | Non-Effervescent paracetamol |  |  |
|----------------------------------|--------------------------|------------------------------|--|--|
| Subject group type               | Subject analysis set     | Subject analysis set         |  |  |
| Number of subjects analysed      | 46                       | 41                           |  |  |
| Units: mmHG                      |                          |                              |  |  |
| number (confidence interval 95%) | 3.59 (1.39 to 5.79)      | -0.33 (-1.78 to 1.13)        |  |  |

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Intention to Treat                                      |
| Statistical analysis description:   |   |
| CROSSOVER DESIGN. Total number of patients 46. All both arms of treatment.<br>We estimated the sample size for a crossover trial with the aim to detect a mean difference in 24-h SBP greater than 2mmHg (minimum clinically relevant difference) assuming a SD of 4.5mmHg. With a two-sided alpha error of 5%, we estimated that 49 patients would need to be enrolled to have a statistical power of 80% considering 15% of dropout rate. |   |
| Comparison groups   | Non-Effervescent paracetamol v Effervescent paracetamol |
| Number of subjects included in analysis   | 87  |
| Analysis specification  | Pre-specified   |
| Analysis type   | superiority <sup>[1]</sup>                              |
| P-value   | = 5   |
| Method  | ANOVA   |
| Parameter estimate  | Mean difference (final values)                          |
| Point estimate  | 2   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | 0   |
| upper limit   | 11  |
| Variability estimate  | Standard deviation                                      |
| Dispersion value  | 4.5   |

Notes:

[1] - Main and secondary analysis was carried out on an intention-to-treat (ITT) basis with patients who fulfilled all the eligibility criteria and had a measurement of the primary outcome at the baseline visit.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All study period.

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 18 |
|--------------------|----|

### Reporting groups

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Effervescent paracetamol |
|-----------------------|--------------------------|

Reporting group description: -

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | Non-Effervescent paracetamol |
|-----------------------|------------------------------|

Reporting group description: -

| Serious adverse events                            | Effervescent paracetamol | Non-Effervescent paracetamol |  |
|---|--------------------------|------------------------------|--|
| Total subjects affected by serious adverse events |                          |                              |  |
| subjects affected / exposed                       | 0 / 46 (0.00%)           | 0 / 41 (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                            | Effervescent paracetamol | Non-Effervescent paracetamol |  |
|---|--------------------------|------------------------------|--|
| Total subjects affected by non-serious adverse events |                          |                              |  |
| subjects affected / exposed                           | 7 / 46 (15.22%)          | 4 / 41 (9.76%)               |  |
| Nervous system disorders                              |                          |                              |  |
| Headache  |                          |                              |  |
| subjects affected / exposed                           | 2 / 46 (4.35%)           | 1 / 41 (2.44%)               |  |
| occurrences (all)                                     | 2                        | 1                            |  |
| Dizziness   |                          |                              |  |
| subjects affected / exposed                           | 2 / 46 (4.35%)           | 1 / 41 (2.44%)               |  |
| occurrences (all)                                     | 2                        | 1                            |  |
| Vertigo   |                          |                              |  |
| subjects affected / exposed                           | 2 / 46 (4.35%)           | 2 / 41 (4.88%)               |  |
| occurrences (all)                                     | 2                        | 2                            |  |
| Respiratory, thoracic and mediastinal disorders       |                          |                              |  |



|   |                                     |                |  |
|---|-------------------------------------|----------------|--|
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all) | Additional description: Common cold |                |  |
|   | 3 / 46 (6.52%)                      | 0 / 41 (0.00%) |  |
|   | 4                                   | 0              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment |
|------------------|-----------|
| 01 June 2011     | New sites |
| 03 October 2011  | New sites |
| 02 August 2012   | New sites |
| 01 February 2013 | New sites |
| 08 May 2013      | New sites |

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Only main results included. See paper for more specified information.

Notes:

---

### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29570512>