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, agarcia@idiapjgol.org
Scientific contact	Ana Garcia-Sangenis, IDIAP Jordi Gol - UEM, +34 934824644, agarcia@idiapjgol.org

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[1]
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
Arm title	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

Arm title	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 - Non effervescent	BA - Non effervescent - 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:	
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:	
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 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 Units: years			
arithmetic mean	66.8	67.1	
standard deviation	± 9.6	± 8.3	-
Gender categorical 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:	
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:	
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:	
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:	
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:	
Crossover study. Difference in 24h SBP when 3 weeks treatment of non effervescent paracetamol vs 3 weeks treatment of effervescent paracetamol. 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. 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. 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:	
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

Statistical analysis title	Intention to Treat

Statistical analysis description:

CROSSOVER DESIGN. Total number of patients 46. All both arms of treatment.
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[1]
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	Additional description: Common cold		
subjects affected / exposed	3 / 46 (6.52%)	0 / 41 (0.00%)	
occurrences (all)	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