Clinical trial results:
Efectos de la administración de ornitina-fenilacetato (OCR-002) en pacientes con cirrosis y hemorragia digestiva alta. Effects of the administration of ornithine phenylacetate (OP, OCR-002) in patients with cirrhosis and upper gastrointestinal bleeding

Summary

EudraCT number	2009-017819-16
Trial protocol	ES
Global end of trial date	24 March 2015

Results information

Result version number	v1 (current)
This version publication date	14 October 2021
First version publication date	14 October 2021

Trial information

Trial identification

Sponsor protocol code	OP-GIB

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	VHIR
Sponsor organisation address	Passeig Vall Hebron 119-129, Barcelona, Spain, 08035
Public contact	Joaquin Lopez-Soriano, VHIR, joaquin.lopez.soriano@vhir.org
Scientific contact	Juan Cordoba, VHIR, jcordoba@vhebron.net

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	24 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 March 2015
Global end of trial reached?	Yes
Global end of trial date	24 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluar la eficacia del fármaco experimental para reducir la concentración plasmática de amoníaco que sigue a una hemorragia digestiva en pacientes con cirrosis hepática

Protection of trial subjects:

Patients were admitted to a semi-intensive care unit (Bleeding Unit) for at least 48 hours, until clinical stability was established. After this period of time, patients were transferred to a general medicine ward.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 October 2011
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: 38
Worldwide total number of subjects	38
EEA total number of subjects	38

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)	38
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment	
Recruitment details: -	

Pre-assignment	
Screening details: -	

Pre-assignment period milestones	
Number of subjects started	38
Number of subjects completed	38

Period 1	
Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms	
Are arms mutually exclusive?	Yes
Arm title	Ornithine
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Ornithine Phenilacetate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administration of OP (OCR-002) during 5 days in addition to standard treatment of gastrointestinal bleeding

Arm title	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Saline 0.9%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administration of control infusion (saline infusion) during 5 days in addition to standard treatment of gastrointestinal bleeding.

Number of subjects in period 1	Ornithine	Placebo
Started	18	20
Completed	18	20

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	38	38	
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			
median	56		
standard deviation	± 11	-	
Gender categorical Units: Subjects			
Female	12	12	
Male	26	26	

End points

End points reporting groups

Reporting group title	Ornithine
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Decrease Ammonium in plasma

End point title	Decrease Ammonium in plasma
End point description:	
The primary outcome was a decrease in average venous plasma ammonia at 24 hours. Ammonia was measured in a Cobas 6000 analyzer (Roche Diagnostics Indianapolis, IN, USA) by standard methodology.	
End point type	Primary
End point timeframe:	
24 hours	

End point values	Ornithine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: micromole(s)/litre				
median (confidence interval 5%)	-20.40 (-39.20 to -2.80)	-11.88 (-36.75 to -2.35)		

Statistical analyses

Statistical analysis title	Ammonia levels plasma
Comparison groups	Ornithine v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)

Secondary: Plasma Phenylacetate 120h

End point title	Plasma Phenylacetate 120h
End point description:	
End point type	Secondary

End point timeframe:
120 hours

End point values	Ornithine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: micromole(s)/litre				
arithmetic mean (standard deviation)	110.5 (± 131.4)	1.1 (± 1.8)		

Statistical analyses

Statistical analysis title	Phenylacetate plasma
Comparison groups	Placebo v Ornithine
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided

Secondary: PAGN urine

End point title	PAGN urine

End point description:
Accumulated mmol in urine at 120 hours

End point type	Secondary

End point timeframe:
120 hours

End point values	Ornithine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: micromole(s)/litre				
arithmetic mean (standard deviation)	190 (± 85)	9.5 (± 9.8)		

Statistical analyses

Statistical analysis title	Accumulated PAGN urine
Comparison groups	Ornithine v Placebo

Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 1-sided

Secondary: PAGN/Creatinine urine

End point title	PAGN/Creatinine urine

End point description:

End point type	Secondary

End point timeframe:

120 hours

End point values	Ornithine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: mmol/mol				
arithmetic mean (standard deviation)	3177 (± 1400)	178 (± 232)		

Statistical analyses

Statistical analysis title	PAGN/Creatinine in urine
Comparison groups	Ornithine v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 1-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events: All the study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups	
Reporting group title	Total adverse events

Reporting group description: -

Serious adverse events	Total adverse events		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 38 (26.32%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subdural haematoma			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Hemorrhagic shock			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Upper gastrointestinal haemorrhage			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic encephalopathy			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory tract infection			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Total adverse events		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 38 (50.00%)		
Vascular disorders			
Edema			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Anxiety			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Lymphopenia			

subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Neutropenia			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Hypertension			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	9 / 38 (23.68%)		
occurrences (all)	9		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Hepatobiliary disorders			
Ascites			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Cramps			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	10 / 38 (26.32%)		
occurrences (all)	10		
Hyponatraemia			

subjects affected / exposed	5 / 38 (13.16%)		
occurrences (all)	5		
Alkaline Phosphatase increased			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Hyperglycaemia			
subjects affected / exposed	13 / 38 (34.21%)		
occurrences (all)	13		
Asthenia			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Hypocalcaemia			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		

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

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

The current study did not achieve the primary objective, probably due to individual variability, a small number of patients included and mainly, too low a dose of OP administered.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27803737