



Clinical trial results: A Pilot Study to Evaluate the Safety, Tolerability and Efficacy of Obeticholic Acid (INT-747) for the Treatment of Portal Hypertension (PESTO)

Summary

EudraCT number	2010-023241-29
Trial protocol	GB BE AT
Global end of trial date	20 January 2014

Results information

Result version number	v1 (current)
This version publication date	09 June 2019
First version publication date	09 June 2019

Trial information

Trial identification

Sponsor protocol code	747-204
-----------------------	---------

Additional study identifiers

ISRCTN number	ISRCTN22662520
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Intercept Pharmaceuticals, Inc.
Sponsor organisation address	4760 Eastgate Mall, San Diego/CA, United States, 92121
Public contact	Medical Information , Intercept Pharmaceuticals, Inc., medinfo@interceptpharma.com
Scientific contact	Christian Weyer, M.D., M.A.S. Executive Vice President, R&D, Intercept Pharmaceuticals, Inc., christian.weyer@interceptpharma.com

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	30 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 December 2013
Global end of trial reached?	Yes
Global end of trial date	20 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this trial were to assess the effects of obeticholic acid (OCA) in subjects with cirrhosis on safety and tolerability and portal hypertension.

Protection of trial subjects:

The trial was conducted in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All the local regulatory requirements pertinent to safety of trial subjects have also been followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 August 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 4
Worldwide total number of subjects	34
EEA total number of subjects	34

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)	31
From 65 to 84 years	3

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from in-patient or out-patient hospital clinics. The first subject was screened 03 August 2011 and the last subject was screened 16 December 2013.

Pre-assignment

Screening details:

Subjects were screened within a permitted window of 7 days prior to dosing to assess and confirm eligibility. There was no mandated washout and no run-in period.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	10 mg OCA Safety Cohort

Arm description:

Subjects received 10 milligrams (mg) OCA once daily.

Arm type	Experimental
Investigational medicinal product name	OCA
Investigational medicinal product code	INT-747
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received 10 mg OCA, once daily, for approximately 7 consecutive days; a minimum of 6 days and a maximum of 12 days were allowed. Each dose administered was made up of 1 capsule per day, taken in the morning, at approximately the same time each day.

Arm title	25 mg OCA Safety Cohort
------------------	-------------------------

Arm description:

Subjects received 25 mg OCA once daily.

Arm type	Experimental
Investigational medicinal product name	OCA
Investigational medicinal product code	INT-747
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received 25 mg OCA, once daily, for approximately 7 consecutive days; a minimum of 6 days and a maximum of 12 days were allowed. Each dose administered was made up of 1 capsule per day, taken in the morning, at approximately the same time each day.

Arm title	10 mg OCA Efficacy Cohort
------------------	---------------------------

Arm description:

Subjects received 10 mg OCA once daily. Subjects in the Efficacy Cohort had hepatic venous pressure gradient (HVPG) measurements.

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

Investigational medicinal product name	OCA
Investigational medicinal product code	INT-747
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 10 mg OCA, once daily, for approximately 7 consecutive days; a minimum of 6 days and a maximum of 12 days were allowed. Each dose administered was made up of 1 capsule or tablet per day, taken in the morning, at approximately the same time each day.

Arm title	25 mg OCA Efficacy Cohort
------------------	---------------------------

Arm description:

Subjects received 25 mg OCA once daily. Subjects in the Efficacy Cohort had HVPG measurements.

Arm type	Experimental
Investigational medicinal product name	OCA
Investigational medicinal product code	INT-747
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received 25 mg OCA, once daily, for approximately 7 consecutive days; a minimum of 6 days and a maximum of 12 days were allowed. Each dose administered was made up of 1 capsule per day, taken in the morning, at approximately the same time each day.

Number of subjects in period 1^[1]	10 mg OCA Safety Cohort	25 mg OCA Safety Cohort	10 mg OCA Efficacy Cohort
Started	4	5	16
Received at least 1 dose of study drug	4	5	16
Completed	4	4	16
Not completed	0	1	0
Adverse event, non-fatal	-	1	-

Number of subjects in period 1^[1]	25 mg OCA Efficacy Cohort
Started	8
Received at least 1 dose of study drug	8
Completed	8
Not completed	0
Adverse event, non-fatal	-

Notes:

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

Justification: One subject was enrolled in the study but never treated and was not included in the subject disposition table.

Baseline characteristics

Reporting groups

Reporting group title	10 mg OCA Safety Cohort
Reporting group description: Subjects received 10 milligrams (mg) OCA once daily.	
Reporting group title	25 mg OCA Safety Cohort
Reporting group description: Subjects received 25 mg OCA once daily.	
Reporting group title	10 mg OCA Efficacy Cohort
Reporting group description: Subjects received 10 mg OCA once daily. Subjects in the Efficacy Cohort had hepatic venous pressure gradient (HVPG) measurements.	
Reporting group title	25 mg OCA Efficacy Cohort
Reporting group description: Subjects received 25 mg OCA once daily. Subjects in the Efficacy Cohort had HVPG measurements.	

Reporting group values	10 mg OCA Safety Cohort	25 mg OCA Safety Cohort	10 mg OCA Efficacy Cohort
Number of subjects	4	5	16
Age categorical			
All subjects who received at least 1 dose of study drug.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	3	4	15
From 65-84 years	1	1	1
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	52.0	56.2	52.6
standard deviation	± 9.76	± 6.18	± 7.05
Gender categorical			
Units: Subjects			
Female	2	2	6
Male	2	3	10

Reporting group values	25 mg OCA Efficacy Cohort	Total	
Number of subjects	8	33	
Age categorical			
All subjects who received at least 1 dose of study drug.			
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)	8	30	
From 65-84 years	0	3	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	46.1		
standard deviation	± 10.95	-	
Gender categorical			
Units: Subjects			
Female	1	11	
Male	7	22	

End points

End points reporting groups

Reporting group title	10 mg OCA Safety Cohort
Reporting group description:	Subjects received 10 milligrams (mg) OCA once daily.
Reporting group title	25 mg OCA Safety Cohort
Reporting group description:	Subjects received 25 mg OCA once daily.
Reporting group title	10 mg OCA Efficacy Cohort
Reporting group description:	Subjects received 10 mg OCA once daily. Subjects in the Efficacy Cohort had hepatic venous pressure gradient (HVPG) measurements.
Reporting group title	25 mg OCA Efficacy Cohort
Reporting group description:	Subjects received 25 mg OCA once daily. Subjects in the Efficacy Cohort had HVPG measurements.
Subject analysis set title	10 mg OCA Safety Cohort
Subject analysis set type	Safety analysis
Subject analysis set description:	Subjects who received at least 1 dose of treatment with 10 mg OCA in the safety cohort.
Subject analysis set title	25 mg OCA Safety Cohort
Subject analysis set type	Safety analysis
Subject analysis set description:	Subjects who received at least 1 dose of treatment with 25 mg OCA in the safety cohort.
Subject analysis set title	10 mg OCA Efficacy Cohort
Subject analysis set type	Sub-group analysis
Subject analysis set description:	Subjects who received at least 6 days of treatment with 10 mg OCA and who had both baseline and on-treatment HPVg assessments.
Subject analysis set title	25 mg OCA Efficacy Cohort
Subject analysis set type	Sub-group analysis
Subject analysis set description:	Subjects who received at least 6 days of treatment with 25 mg OCA and who had both baseline and on-treatment HPVg assessments.

Primary: Number Of Subjects With Treatment-emergent Adverse Events (TEAEs)

End point title	Number Of Subjects With Treatment-emergent Adverse Events (TEAEs) ^[1]
End point description:	TEAEs were defined as those AEs with onset after the first dose of OCA or existing events that worsened after the first dose during the study. Events reported with a partial onset date (for example, month and year were reported but the day was missing) were considered to be treatment-emergent if it could not be confirmed that the event onset was prior to the first dose of OCA, based on the available date entries.
End point type	Primary
End point timeframe:	From Day 1 after dosing through end of study; includes 6 to 12 days of treatment and 2 to 4 weeks of post-dosing follow-up

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical analysis, that is, hypothesis testing, was performed to compare treatment groups. This study was exploratory in nature; descriptive statistics were tabulated by cohort and study part and reviewed to evaluate all study end points.

End point values	10 mg OCA Safety Cohort	25 mg OCA Safety Cohort	10 mg OCA Efficacy Cohort	25 mg OCA Efficacy Cohort
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	5	16	8
Units: subjects				
number (not applicable)				
At least 1 TEAE	3	4	12	6
Any serious TEAE	0	0	0	0
Study discontinuation due to TEAE	0	1	0	0
TEAE leading to death	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Percentage Of Responders, As Assessed By HVPG

End point title	Percentage Of Responders, As Assessed By HVPG ^[2]
-----------------	--

End point description:

A subject who had improvement in portal pressure, as assessed by a reduction of $\geq 15\%$ in HVPG, compared to baseline, or having a HVPG < 12 mmHg after approximately 7 days of treatment was defined as a responder. A window of 6 to 12 days was allowed for treatment and HVPG was collected when the subject discontinued treatment.

End point type	Primary
----------------	---------

End point timeframe:

From baseline through end of treatment (6 to 12 days)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical analysis, that is, hypothesis testing, was performed to compare treatment groups. This study was exploratory in nature; descriptive statistics were tabulated by cohort and study part and reviewed to evaluate all study end points.

End point values	10 mg OCA Efficacy Cohort	25 mg OCA Efficacy Cohort		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	8		
Units: percentage of subjects				
number (confidence interval 95%)	31.3 (11.0 to 58.7)	50.0 (15.7 to 84.3)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 after dosing through end of study; includes 6 to 12 days of treatment and 2 to 4 weeks of post-dosing follow-up.

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	15

Reporting groups

Reporting group title	10 mg OCA Safety Cohort
-----------------------	-------------------------

Reporting group description:

Subjects were to receive 10 mg OCA once daily.

Reporting group title	25 mg OCA Safety Cohort
-----------------------	-------------------------

Reporting group description:

Subjects were to receive 25 mg OCA once daily.

Reporting group title	10 mg OCA Efficacy Cohort
-----------------------	---------------------------

Reporting group description:

Subjects were to receive 10 mg OCA once daily. Subjects in the Efficacy Cohort had hepatic venous pressure gradient (HPVG) measurements.

Reporting group title	25 mg OCA Efficacy Cohort
-----------------------	---------------------------

Reporting group description:

Subjects were to receive 25 mg OCA once daily. Subjects in the Efficacy Cohort had hepatic venous pressure gradient (HPVG) measurements.

Serious adverse events	10 mg OCA Safety Cohort	25 mg OCA Safety Cohort	10 mg OCA Efficacy Cohort
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Lacunar infarction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	25 mg OCA Efficacy Cohort		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Nervous system disorders			
Lacunar infarction			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	10 mg OCA Safety Cohort	25 mg OCA Safety Cohort	10 mg OCA Efficacy Cohort
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 4 (75.00%)	3 / 5 (60.00%)	12 / 16 (75.00%)
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Product taste abnormal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Tooth fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Tachycardia			

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 16 (6.25%) 1
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	3 / 16 (18.75%) 3
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 16 (6.25%) 1
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	3 / 16 (18.75%) 3
Ascites subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 16 (6.25%) 1
Abdominal pain subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	0 / 16 (0.00%) 0
Dyspepsia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 16 (6.25%) 1
Vomiting subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 16 (6.25%) 1
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	2 / 16 (12.50%) 2
Rash subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	0 / 16 (0.00%) 0
Rash macular subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 16 (0.00%) 0
Renal and urinary disorders			

Renal colic subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 16 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 16 (6.25%) 1
Muscle spasms subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	0 / 16 (0.00%) 0
Infections and infestations			
Lower respiratory tract infection subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 5 (0.00%) 0	1 / 16 (6.25%) 1
Rhinitis subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 5 (0.00%) 0	0 / 16 (0.00%) 0
Metabolism and nutrition disorders			
Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 5 (20.00%) 1	0 / 16 (0.00%) 0

Non-serious adverse events	25 mg OCA Efficacy Cohort		
Total subjects affected by non-serious adverse events subjects affected / exposed	6 / 8 (75.00%)		
Vascular disorders			
Flushing subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
General disorders and administration site conditions			
Product taste abnormal subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Immune system disorders			
Seasonal allergy subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		

Investigations Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Injury, poisoning and procedural complications Tooth fracture subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Cardiac disorders Palpitations subjects affected / exposed occurrences (all) Tachycardia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0 0 / 8 (0.00%) 0		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Ascites subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Vomiting	0 / 8 (0.00%) 0 1 / 8 (12.50%) 1 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 0		

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	4 / 8 (50.00%) 4		
Rash subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 2		
Rash macular subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Renal and urinary disorders Renal colic subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Muscle spasms subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Infections and infestations Lower respiratory tract infection subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Rhinitis subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2011	Revision to include electrocardiographs at Screening and on-study
08 September 2011	<ul style="list-style-type: none">• Modified to include 24 hour urine collection and urinary creatinine clearance• Modified to add Exclusion criterion for known iodine allergy or sensitivity to contrast media• Inclusion Criteria modified to clarify diagnosis of portal hypertension• Modified to add in additional serious adverse events causality terms• Revision to Patient Information Sheet (PIS)/Informed Consent (IC) for efficacy cohort to include x-rays and radiation exposure• Modified to add conjugated bilirubin
06 August 2012	<ul style="list-style-type: none">• Modified to include that investigational product can be provided as either capsules or tablets• Inclusion Criteria modified to allow gallstones
19 June 2013	<ul style="list-style-type: none">• Modified to include alcohol abstinence in Inclusion Criteria• Modified to exclude alcoholic hepatitis with sepsis within 3 months of starting the study• PIS/IC modified to consent for additional safety samples

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported