Clinical trial results:
Clinical Study of the BreathID® LF System to train the algorithm for the ^{13}C-Methacetin Breath Test (MBT) in assessment of Portal Hypertension in Patients with Compensated Liver Cirrhosis

Summary

EudraCT number	2014-002037-59
Trial protocol	ES
Global end of trial date	11 January 2019

Results information

Result version number	v1 (current)
This version publication date	12 May 2021
First version publication date	12 May 2021

Trial information

Trial identification

Sponsor protocol code	CSPH-EX-0414

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02143778
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Exalenz Bioscience
Sponsor organisation address	4 Hamaayan Street, Modiin, Israel, 7177872
Public contact	Avraham Hershkowitz, Exalenz Bioscience, 972 546605412, avrahamh@exalenz.com
Scientific contact	Avraham Hershkowitz, Exalenz Bioscience, 972 546605412, avrahamh@exalenz.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	13 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 October 2017
Global end of trial reached?	Yes
Global end of trial date	11 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to develop an algorithm and its cut-off to detect CSPH, defined as HVPG ≥10mmHg, based on the MBT.

Protection of trial subjects:

This test is a diagnostic test with 75mg of Methacetin (similar to paracetamol) used as as the testing substrate. No safety precautions were needed other than verifying that subject is not sensitive to paracetamol.

Background therapy:

The gold standard for measuring portal hypertension in the liver is hepatic venous pressure gradient (HVPG). A measure of 12 or more mmHg is classified as severe portal hypertension (SPH).

Evidence for comparator:

HVPG is standard of care in several countries for patients with cirrhotic livers. Several peer reviewed papers have been published on this subject as well. The proposed Methacetin Breath Test correlates to this invasive method in assessing the probability of SPH.

Actual start date of recruitment	01 September 2014
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: 158
Country: Number of subjects enrolled	United States: 39
Country: Number of subjects enrolled	France: 40
Country: Number of subjects enrolled	Switzerland: 9
Worldwide total number of subjects	246
EEA total number of subjects	198

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)	161
From 65 to 84 years	85
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

At least 200 consecutive compensated cirrhotic patients , defined as cirrhotic patients without known liver decompensation complications and meeting all inclusion/exclusion criteria were to be enrolled on a walk-in basis of which at least 50 had to be positive for CSPH and at least 50 had to be negative for CSPH.

Pre-assignment

Screening details:

3. Known chronic liver disease with cirrhosis confirmed by either:
a. liver biopsy or
b. clinical (palpable left lobe, splenomegaly) and laboratory (platelets <150,000/mm3 or albumin< 3.8 g/dL, or INR >1.3) evidence of cirrhosis and/or
c. imaging studies by abdominal sonography, computer assisted axial tomography, or magnetic resonance imaging,

Period 1

Period 1 title	Initial Visit (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Blinding implementation details:

Methacetin Breath Test results were withheld from investigator

Arms

Arm title	General

Arm description:

General walk- in population

Arm type	Experimental
Investigational medicinal product name	Methacetin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Single use bottle of solution to be administered orally by pouring into a cup, after 8 hour fasting.

Number of subjects in period 1	General
Started	246
Completed	243
Not completed	3
Lost to follow-up	3

Baseline characteristics

Reporting groups

Reporting group title	Initial Visit

Reporting group description: -

Reporting group values	Initial Visit	Total	
Number of subjects	246	246	
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	60.4		
full range (min-max)	23.4 to 81.6	-	
Gender categorical Units: Subjects			
Female	93	93	
Male	153	153	

Subject analysis sets

Subject analysis set title	FA
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects that were enrolled in this study will be included in this analysis

Reporting group values	FA		
Number of subjects	246		
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			

From 65-84 years 85 years and over			

Age continuous Units: years median full range (min-max)	 60.4 23.4 to 81.6		
Gender categorical Units: Subjects			
Female Male	153 93		

End points

End points reporting groups

Reporting group title	General
Reporting group description:	
General walk- in population	
Subject analysis set title	FA
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects that were enrolled in this study will be included in this analysis	

Primary: Clinically Significant Portal Hypertension

End point title	Clinically Significant Portal Hypertension[1]
End point description:	
Methacetin Breath Test with a pre-defined cutoff was compared to HVPG for determination of clinically significant portal hypertension (CSPH) (defined as HVPG >10mmHg)	
End point type	Primary
End point timeframe:	
One time diagnostic test for duration of 1 hour with 48 hour safety 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: This study was done for feasibility purposes only as a training trial for a validation trial design and study. No specific analyses were performed other the assessing area under the curve receiver operating curves, enabling validation protocol design.	

End point values	General	FA		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	246	246		
Units: Accuracy	246	246		

Statistical analyses

No statistical analyses for this end point

Secondary: Severe Portal Hypertension

End point title	Severe Portal Hypertension
End point description:	
Methacetin Breath Test with pre determined cutoff compared to HVPG to determine severe portal hypertension (SPH) (defined as HVPG>12)	
End point type	Secondary
End point timeframe:	
One time test with duration of 1 hour with a 48 hour safety follow up.	

End point values	General	FA		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	246	246		
Units: Accuracy	246	246		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 48 hours- from beginning of test that lasts 1 hour and a 48 hour follow up for possible safety issues.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	1

Reporting groups	
Reporting group title	FA set
Reporting group description: The reporting will include the full analysis set	

Serious adverse events	FA set		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 246 (0.41%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Severe Diarrhea			
subjects affected / exposed	1 / 246 (0.41%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0.5 %

Non-serious adverse events	FA set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 246 (0.81%)		
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	2 / 246 (0.81%)		
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

None reported