Clinical trial results:
A Phase 2a, randomized, double-blind, placebo-controlled study of oral FXR modulator EYP001a combined with nucleos(t)ide analogues (NA) in virologically suppressed chronic hepatitis B patients to improve functional cure rates

Summary

EudraCT number	2019-001629-28
Trial protocol	PL
Global end of trial date	25 November 2021

Results information

Result version number	v1 (current)
This version publication date	07 September 2022
First version publication date	07 September 2022

Trial information

Trial identification

Sponsor protocol code	EYP001-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04465916
WHO universal trial number (UTN)	-
Other trial identifiers	IND number: 142570

Notes:

Sponsors

Sponsor organisation name	Enyo Pharma SA
Sponsor organisation address	60 avenue Rockefeller, Lyon, France, 69008
Public contact	Chief Medical Officer, ENYO Pharma SA, +33 4 3770 0219, ps@enyopharma.com
Scientific contact	Chief Medical Officer, ENYO Pharma SA, +33 4 3770 0219, ps@enyopharma.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	25 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 June 2021
Global end of trial reached?	Yes
Global end of trial date	25 November 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine the effect of EYP001a on top of NA (SOC therapy) on HBsAg plasma levels

Protection of trial subjects:

The Clinical Study Protocol (CSP), informed consent documents, and any other appropriate study-related documents were reviewed and approved by an IEC/IRB.

Background therapy:

ENYO Pharma is developing EYP001a, a selective, synthetic, non-bile salt, carboxylic acid agonist, or modulator, of the farnesoid X receptor (FXR), for the treatment of chronic hepatitis B (CHB) virus infections. Chronic liver diseases are major public health problems. Current worldwide estimations show that 844 million people have chronic liver diseases, with a mortality rate of 2 million deaths per year. Patients with chronic hepatitis B virus infection have increased rates of liver-related mortality due to the development of complications, including fibrosis, cirrhosis, and hepatocellular carcinoma. Therefore, there is an urgent need for improved treatment options for chronic liver diseases.

Evidence for comparator:

Placebo

Actual start date of recruitment	12 May 2020
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	Australia: 5
Country: Number of subjects enrolled	Hong Kong: 2
Country: Number of subjects enrolled	Korea, Republic of: 19
Worldwide total number of subjects	26
EEA total number of subjects	0

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)	26
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was open to chronic HBV carriers with no recent (3 months) history of any clinically significant conditions, which, in the opinion of the investigator, would jeopardize the safety of the patient or impact the validity of the study results. Study planned to randomized 49 patients and 26 were finally randomized.

Pre-assignment

Screening details:

Screening procedures were applied to each patient who signs an informed consent form: eligibility based inclusion and exclusion criteria. Patient screening occured no more than 90 days prior to the Day 1 visit. Eligible patients undergone further assessments on Day 1 to qualify for study drug .

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo and NA

Arm description:

Placebo + NA

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo once a day

Investigational medicinal product name	Nucleos(t)ide analogue
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

NA treatment (ETV or TDF) provided in combination with placebo as a SOC per the dosing guidelines presented in the country-specific label(s). Entecavir (ETV) 0.5 mg daily (or per country specific label) or Tenofovir Disoproxil Fumarate (TDF) 300 mg daily which is equivalent to 245 mg of tenofovir disoproxil given per country specific label). Patients continued to receive NA treatment during the follow-up phase as well.

Arm title	EYP001a and NA

Arm description:

EYP001a 200mg + NA

Arm type	Experimental

Investigational medicinal product name	EYP001a
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

200 mg of EYP001a once a day

Investigational medicinal product name	Nucleos(t)ide analogue
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

NA treatment (ETV or TDF) provided in combination with EYP001a as a SOC per the dosing guidelines presented in the country-specific label(s). Entecavir (ETV) 0.5 mg daily (or per country specific label) or Tenofovir Disoproxil Fumarate (TDF) 300 mg daily which is equivalent to 245 mg of tenofovir disoproxil given per country specific label). Patients continued to receive NA treatment during the follow-up phase as well.

Number of subjects in period 1	Placebo and NA	EYP001a and NA
Started	7	19
Completed	6	19
Not completed	1	0
Consent withdrawn by subject	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo and NA
Reporting group description: Placebo + NA	
Reporting group title	EYP001a and NA
Reporting group description: EYP001a 200mg + NA	

Reporting group values	Placebo and NA	EYP001a and NA	Total
Number of subjects	7	19	26
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	46.29	45.16	
standard deviation	± 8.46	± 8.32	-
Gender categorical Units: Subjects			
Female	1	5	6
Male	6	14	20
Race Units: Subjects			
Asian	5	19	24
Black or african american	1	0	1
White	1	0	1
Ethnicity Units: Subjects			
Not hispanic or latino	6	16	22
Unknown	1	3	4
Weight Units: kg			
arithmetic mean	82.857	68.821	
standard deviation	± 21.084	± 11.293	-
Height Units: cm			
arithmetic mean	172.529	168.763	

standard deviation	± 11.342	± 9.333	-

End points

End points reporting groups	
Reporting group title	Placebo and NA
Reporting group description: Placebo + NA	
Reporting group title	EYP001a and NA
Reporting group description: EYP001a 200mg + NA	

Primary: HBsAg decline	
End point title	HBsAg decline
End point description:	
End point type	Primary
End point timeframe: From baseline to week 16	

End point values	Placebo and NA	EYP001a and NA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	19		
Units: log10				
least squares mean (standard error)	-0.07 (± 0.03)	-0.03 (± 0.02)		

Statistical analyses

Statistical analysis title	General linear model for repeated measures
Comparison groups	Placebo and NA v EYP001a and NA
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Mixed models analysis

Secondary: Virologic failure rate of HBV DNA	
End point title	Virologic failure rate of HBV DNA
End point description:	
End point type	Secondary

End point timeframe:
Week 16

End point values	Placebo and NA	EYP001a and NA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	19		
Units: patients number				
Week 16	0	0		
Week 20	0	0		
Week 28	0	0		
Week 40	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: After the first dose of study drug until W40	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	23
Reporting groups	
Reporting group title	Placebo and NA
Reporting group description: Placebo + NA	
Reporting group title	EYP001a and NA
Reporting group description: EYP001a 200mg + NA	

Serious adverse events	Placebo and NA	EYP001a and NA	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	0 / 19 (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	Placebo and NA	EYP001a and NA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 7 (42.86%)	17 / 19 (89.47%)	
Investigations			
Serum ferritin decreased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
White blood cell count decreased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Flushing			

subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	1 / 7 (14.29%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Syncope			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	2	
Influenza like illness			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Vaccination site discomfort			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Abdominal pain lower			
subjects affected / exposed	1 / 7 (14.29%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Chronic gastritis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	0 / 7 (0.00%)	3 / 19 (15.79%)	
occurrences (all)	0	4	
Faeces discoloured			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Hiatus hernia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	0 / 7 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Oesophagitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Emphysema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Rhinorrhoea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	2	
Throat irritation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Oropharyngeal pain			

subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 7 (14.29%)	15 / 19 (78.95%)	
occurrences (all)	1	19	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Muscular weakness			
subjects affected / exposed	0 / 7 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	3	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 July 2019	• Shortening treatment period from 24 weeks to 16 weeks and increased frequency of safety monitoring to every 2 weeks during treatment period. • Expand DSMC safety overview and incorporate futility rules whereby the DSMC would stop the study after the DSMC review meeting when 50% of subjects reach Week 12 if there is no evidence of vonafexor benefit. • Study stopping rules expanded and DSMC oversight increased.
17 July 2019	• Treatment stopping rules modified such that treatment will be suspended for SAEs considered also as "possibly related" to study drug.
09 August 2019	• Discontinuation criteria in event of drug-induced liver injury updated to comply with inclusion criteria of ALT or AST ≤ 2 × upper limit of normal (ULN)
22 January 2020	• The daily oral vonafexor dose to be administered for 16 weeks was reduced from 400 mg QD (two 200 mg tablets) to 200 mg QD (one 200 mg tablet). • Timepoint Week 40 of maintenance was added to secondary endpoints HBV-pgRNA decline (Δ log10) and HBcrAg decline (Δ log10).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
26 February 2021	The DSMC review meeting was held to review preliminary results of 26 out of 49 planned subjects randomized. No effect on virology markers was observed when vonafexor was administered on top of NAs in the studied population. Based on outcomes of this meeting, ENYO Pharma decided that new randomizations were to be stopped. Despite vonafexor being well tolerated, the lack of an impact on virology markers shifts the risk benefit ratio for subjects to be randomized, and it was not considered in their interest to start treatment. Already randomized subjects were however maintained in the study with no changes to be followed up to Week 40 per protocol to gather long-term safety data in CHB aviremic subjects.	-

Notes:

Limitations and caveats

None reported