Clinical trial results:
A Phase 2a, Randomized, Double-Blind, Multicenter, Placebo Controlled Study to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of EYP001a in Patients With Nonalcoholic Steatohepatitis

Summary

EudraCT number	2018-003119-22
Trial protocol	BE FR GB
Global end of trial date	06 July 2021

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	EYP001-202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03812029
WHO universal trial number (UTN)	-

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, 33 437 700 219, ps@enyopharma.com
Scientific contact	Chief Medical Officer, ENYO Pharma SA, 33 437 700 219, 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	06 July 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 June 2021
Global end of trial reached?	Yes
Global end of trial date	06 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to determine the efficacy and safety profiles of EYP001a versus placebo on liver fat content (LFC) from baseline to Week 12 in patients with NASH.

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:

Vonafexor is an agonist of the FXR, a key regulator of bile, lipid, and glucose metabolism, currently under clinical investigation as a new therapy for a functional cure of chronic HBV infection. In an experimental rodent model of NASH, vonafexor analogue has been shown to reduce liver steatosis, inflammation, apoptosis, and fibrosis. Moreover, bile acid activation of the FXR improved the histological features of NASH in patients with noncirrhotic NASH.
The purpose of this Phase 2a study was to assess the effects of vonafexor compared with placebo on markers of LFC, inflammation, and fibrosis with respect to safety, tolerability, PK, PD, and lipid/metabolic profiles in subjects with a NASH diagnosis compatible with Stage F2 to F3 fibrosis.

Evidence for comparator:

Placebo.

Actual start date of recruitment	30 January 2019
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	Puerto Rico: 3
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	United States: 93
Worldwide total number of subjects	120
EEA total number of subjects	19

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	90
From 65 to 84 years	30
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Males, females aged 18y or older provided informed consent and with a suspected diagnosis of NASH with fibrosis (non invasive testing) or a documented biopsy of Stage F2 to F3 liver fibrosis were enrolled in this study. Part A planned to randomize 24 subjects and 24 were randomized. Part B planned to randomize 90 subjects and 96 were randomized.

Pre-assignment

Screening details:

Following sequence of screening procedures were applied to each patient who signs an informed consent form: eligibility based on clinical and biological inclusion and exclusion criteria; eligibility based on FibroScan criteria; confirmation of eligibility based on MRI-PDFF results. Screening was up to 12 weeks prior to Day 1.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A Placebo

Arm description:

Part A Placebo

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 twice a day

Arm title	Part A EYP001a pooled

Arm description:

Part A EYP001a pooled 100mg BID, 200mg QD and 400mg QD

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

Dosage and administration details:

EYP001a once or twice a day according to treatment arms

Arm title	Part B Placebo

Arm description:

Part B Placebo

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

Arm title	Part B EYP001a 100mg

Arm description:
Part B EYP001a 100mg

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

Dosage and administration details:
EYP001a once a day

Arm title	Part B EYP001a 200mg

Arm description:
Part B EYP001a 200mg

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

Dosage and administration details:
EYP001a once a day

Number of subjects in period 1	Part A Placebo	Part A EYP001a pooled	Part B Placebo
Started	7	17	32
Completed	5	7	32
Not completed	2	10	0
Stopping rules	-	1	-
Consent withdrawn by subject	1	-	-
Adverse event, non-fatal	-	9	-
Lost to follow-up	-	-	-
Protocol deviation	1	-	-

Number of subjects in period 1	Part B EYP001a 100mg	Part B EYP001a 200mg
Started	31	33
Completed	25	23
Not completed	6	10
Stopping rules	-	-

Consent withdrawn by subject	2	2
Adverse event, non-fatal	3	5
Lost to follow-up	-	3
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Part A Placebo
Reporting group description:	
Part A Placebo	
Reporting group title	Part A EYP001a pooled
Reporting group description:	
Part A EYP001a pooled 100mg BID, 200mg QD and 400mg QD	
Reporting group title	Part B Placebo
Reporting group description:	
Part B Placebo	
Reporting group title	Part B EYP001a 100mg
Reporting group description:	
Part B EYP001a 100mg	
Reporting group title	Part B EYP001a 200mg
Reporting group description:	
Part B EYP001a 200mg	

Reporting group values	Part A Placebo	Part A EYP001a pooled	Part B Placebo
Number of subjects	7	17	32
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	48.7	56.1	57.3
standard deviation	± 18.4	± 8.9	± 10.3
Gender categorical Units: Subjects			
Female	2	14	18
Male	5	3	14
Ethnicity Units: Subjects			
Hispanic or latino	2	5	6
Not Hispanic or latino	5	12	26
Race Units: Subjects			
American Indian or Alaska native	0	0	0
Asian	0	0	0
Black or African American	0	1	3
Native hawaiian or other pacific islander	0	0	0
White	7	16	29
Other	0	0	0
Height Units: cm			
arithmetic mean	169.0	163.2	168.1
standard deviation	± 7.4	± 9.9	± 9.8

Weight			
Units: kg			
arithmetic mean	112.4	103.4	97.5
standard deviation	± 32.6	± 25.4	± 18.3
BMI			
Units: kg/m2			
arithmetic mean	39.3	38.8	34.3
standard deviation	± 10.2	± 9.0	± 4.3
Waist circumference			
Units: cm			
arithmetic mean	128.9	116.1	112.6
standard deviation	± 31.5	± 16.0	± 13.0

Reporting group values	Part B EYP001a 100mg	Part B EYP001a 200mg	Total
Number of subjects	31	33	120
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	58.1	54.0	
standard deviation	± 13.7	± 11.9	-
Gender categorical			
Units: Subjects			
Female	14	21	69
Male	17	12	51
Ethnicity			
Units: Subjects			
Hispanic or latino	8	10	31
Not Hispanic or latino	23	23	89
Race			
Units: Subjects			
American Indian or Alaska native	0	1	1
Asian	0	0	0
Black or African American	2	1	7
Native hawaiian or other pacific islander	0	0	0
White	26	31	109
Other	3	0	3
Height			
Units: cm			
arithmetic mean	167.1	166.8	
standard deviation	± 8.5	± 10.1	-
Weight			
Units: kg			
arithmetic mean	95.8	98.8	
standard deviation	± 14.0	± 18.4	-
BMI			
Units: kg/m2			
arithmetic mean	34.3	35.4	
standard deviation	± 4.1	± 5.1	-

Waist circumference			
Units: cm			
arithmetic mean	111.4	114.1	
standard deviation	± 8.6	± 11.8	-

End points

End points reporting groups	
Reporting group title	Part A Placebo
Reporting group description: Part A Placebo	
Reporting group title	Part A EYP001a pooled
Reporting group description: Part A EYP001a pooled 100mg BID, 200mg QD and 400mg QD	
Reporting group title	Part B Placebo
Reporting group description: Part B Placebo	
Reporting group title	Part B EYP001a 100mg
Reporting group description: Part B EYP001a 100mg	
Reporting group title	Part B EYP001a 200mg
Reporting group description: Part B EYP001a 200mg	

Primary: Liver Fat Content	
End point title	Liver Fat Content
End point description: Change from baseline to D84	
End point type	Primary
End point timeframe: From baseline to D84	

End point values	Part A Placebo	Part A EYP001a pooled	Part B Placebo	Part B EYP001a 100mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	12	32	28
Units: percent				
least squares mean (confidence interval 95%)	3.9 (-2.5 to 10.4)	-4.7 (-8.5 to -0.9)	-2.3 (-4.0 to -0.6)	-6.3 (-8.1 to -4.5)

End point values	Part B EYP001a 200mg			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: percent				
least squares mean (confidence interval 95%)	-5.4 (-7.2 to -3.6)			

Statistical analyses

Statistical analysis title	Analysis of change from baseline in LFC
Comparison groups	Part B EYP001a 100mg v Part B Placebo v Part B EYP001a 200mg v Part A EYP001a pooled v Part A Placebo
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA

Secondary: glomerular filtration rate part A

End point title	glomerular filtration rate part A[1]
End point description:	
Change from baseline to D84	
End point type	Secondary
End point timeframe:	
From baseline to D84	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Other arms are reported in a separate endpoint.

End point values	Part A Placebo	Part A EYP001a pooled		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	17		
Units: mL/min/1.73m2				
geometric mean (standard deviation)	-4 (± 18.4)	-11.3 (± 12.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Analyse of % change from baseline Liver Fat Content

End point title	Analyse of % change from baseline Liver Fat Content
End point description:	
% change from baseline to D84	
End point type	Secondary
End point timeframe:	
From baseline to D84	

End point values	Part A Placebo	Part A EYP001a pooled	Part B Placebo	Part B EYP001a 100mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	12	32	28
Units: percent				
least squares mean (confidence interval 95%)	11.7 (-28.5 to 51.9)	-25.0 (-48.4 to -1.5)	-10.5 (-19.0 to -2.0)	-30.4 (-39.4 to -21.3)

End point values	Part B EYP001a 200mg			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: percent				
least squares mean (confidence interval 95%)	-25.3 (-34.3 to -16.2)			

Statistical analyses

Statistical analysis title	Analysis of % change from baseline in LFC
Comparison groups	Part B Placebo v Part B EYP001a 100mg v Part B EYP001a 200mg v Part A EYP001a pooled v Part A Placebo
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA

Secondary: Analyse of change from baseline in CT1

End point title	Analyse of change from baseline in CT1
End point description:	
Change from baseline to D84	
End point type	Secondary
End point timeframe:	
From baseline to D84	

End point values	Part A Placebo	Part A EYP001a pooled	Part B Placebo	Part B EYP001a 100mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	12	32	28
Units: msec				
least squares mean (confidence interval 95%)	35.0 (-27.0 to 97.0)	-58.2 (-98.7 to -17.8)	-9.9 (-38.5 to 18.7)	-80.2 (-110.6 to -49.8)

End point values	Part B EYP001a 200mg			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: msec				
least squares mean (confidence interval 95%)	-71.8 (-100.4 to -43.2)			

Statistical analyses

Statistical analysis title	Analysis of change from baseline in CT1
Comparison groups	Part B Placebo v Part B EYP001a 100mg v Part B EYP001a 200mg v Part A Placebo v Part A EYP001a pooled
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA

Secondary: ALT

End point title	ALT

End point description:

Analysis change from baseline to D84

One patient in VONA-200QD arm part B excluded because experienced a serious transaminase increase due to previously undiagnosed auto-immune hepatitis.

End point type	Secondary

End point timeframe:

From baseline to D84

End point values	Part A Placebo	Part A EYP001a pooled	Part B Placebo	Part B EYP001a 100mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	17	32	31
Units: U/L				
least squares mean (confidence interval 95%)	-4.1 (-27.5 to 19.3)	17.7 (1.9 to 33.5)	-11.7 (-18.9 to -4.6)	-16.3 (-24.1 to -8.4)

End point values	Part B EYP001a 200mg			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: U/L				
least squares mean (confidence interval 95%)	-7.5 (-15.3 to 0.4)			

Statistical analyses

Statistical analysis title	Analysis of change from baseline in ALT
Comparison groups	Part B Placebo v Part B EYP001a 100mg v Part B EYP001a 200mg v Part A Placebo v Part A EYP001a pooled
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Secondary: Gamma GT

End point title	Gamma GT

End point description:

Analysis change from baseline to D84

End point type	Secondary

End point timeframe:

From baseline to D84

End point values	Part A Placebo	Part A EYP001a pooled	Part B Placebo	Part B EYP001a 100mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	17	32	31
Units: U/L				
least squares mean (confidence interval 95%)	3.7 (-7.8 to 15.2)	-25.2 (-34.2 to -16.3)	-3.9 (-9.9 to 2.2)	-40.6 (-47.1 to -34.0)

End point values	Part B EYP001a 200mg			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: U/L				
least squares mean (confidence interval 95%)	-34.1 (-40.6 to -27.7)			

Statistical analyses

Statistical analysis title	Analysis of change from baseline in GGT
Comparison groups	Part B Placebo v Part B EYP001a 100mg v Part B EYP001a 200mg v Part A Placebo v Part A EYP001a pooled
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Secondary: Body weight

End point title	Body weight
End point description: Analysis change from baseline to D84	
End point type	Secondary
End point timeframe: From baseline to D84	

End point values	Part A Placebo	Part A EYP001a pooled	Part B Placebo	Part B EYP001a 100mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	17	32	31
Units: kg				
least squares mean (confidence interval 95%)	1.2 (-1.0 to 3.4)	-2.2 (-3.7 to -0.7)	-0.1 (-1.0 to 0.9)	-1.7 (-2.7 to -0.7)

End point values	Part B EYP001a 200mg			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: kg				

least squares mean (confidence interval 95%)	-2.5 (-3.5 to -1.5)			

Statistical analyses

Statistical analysis title	Analysis of change from baseline in body weight
Comparison groups	Part B Placebo v Part B EYP001a 100mg v Part B EYP001a 200mg v Part A Placebo v Part A EYP001a pooled
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Secondary: Waist circumference

End point title	Waist circumference
End point description: Analysis change from baseline to D84	
End point type	Secondary
End point timeframe: From baseline to D84	

End point values	Part A Placebo	Part A EYP001a pooled	Part B Placebo	Part B EYP001a 100mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	17	32	31
Units: cm				
least squares mean (confidence interval 95%)	-1.8 (-5.0 to 1.4)	-2.9 (-5.0 to -0.7)	0.1 (-1.2 to 1.3)	-1.2 (-2.6 to 0.1)

End point values	Part B EYP001a 200mg			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: cm				
least squares mean (confidence interval 95%)	-2.2 (-3.6 to -0.9)			

Statistical analyses

Statistical analysis title	Analysis change from baseline waist circumference
Comparison groups	Part B Placebo v Part B EYP001a 100mg v Part B EYP001a 200mg v Part A Placebo v Part A EYP001a pooled
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Secondary: Waist to hip ratio part B

End point title	Waist to hip ratio part B[2]

End point description:

Analysis change from baseline to D84

End point type	Secondary

End point timeframe:

From baseline to D84

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Other arms are reported in a separate endpoint.

End point values	Part B Placebo	Part B EYP001a 100mg	Part B EYP001a 200mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	31	33	
Units: ratio				
least squares mean (confidence interval 95%)	0.014 (0.001 to 0.026)	-0.017 (-0.031 to -0.003)	-0.010 (-0.024 to 0.004)	

Statistical analyses

Statistical analysis title	Analysis change from baseline waist hip ratio
Comparison groups	Part B Placebo v Part B EYP001a 100mg v Part B EYP001a 200mg
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Secondary: glomerular filtration rate part B

End point title	glomerular filtration rate part B[3]

End point description:

End point type	Secondary

End point timeframe:

Change from baseline to D84

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Other arms are reported in a separate endpoint.

End point values	Part B Placebo	Part B EYP001a 100mg	Part B EYP001a 200mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	31	33	
Units: mL/min/1.73m2				
least squares mean (confidence interval 95%)	-2.7 (-6.6 to 1.2)	6.2 (1.9 to 10.2)	3.2 (-1.2 to 7.7)	

Statistical analyses

Statistical analysis title	Analysis of change from baseline in eGFR
Comparison groups	Part B Placebo v Part B EYP001a 100mg v Part B EYP001a 200mg
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA

Adverse events

Adverse events information	
Timeframe for reporting adverse events: After the first dose of study drug until D96	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	22
Reporting groups	
Reporting group title	Part A Placebo
Reporting group description: Part A Placebo - treatment emergent AE	
Reporting group title	Part A EYP001a pooled
Reporting group description: Part A EYP001a pooled - treatment emergent AE	
Reporting group title	Part B Placebo
Reporting group description: Part B Placebo - treatment emergent AE	
Reporting group title	Part B EYP001a 100mg
Reporting group description: Part B EYP001a 100mg - treatment emergent AE	
Reporting group title	Part B EYP001a 200mg
Reporting group description: Part B EYP001a 200mg - treatment emergent AE	

Serious adverse events	Part A Placebo	Part A EYP001a pooled	Part B Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	0 / 17 (0.00%)	1 / 32 (3.13%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Transaminases increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 17 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 7 (0.00%)	0 / 17 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 7 (0.00%)	0 / 17 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 17 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 7 (0.00%)	0 / 17 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part B EYP001a 100mg	Part B EYP001a 200mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 31 (3.23%)	2 / 33 (6.06%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Transaminases increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Part A Placebo	Part A EYP001a pooled	Part B Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 7 (57.14%)	16 / 17 (94.12%)	22 / 32 (68.75%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 17 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 7 (14.29%)	1 / 17 (5.88%)	1 / 32 (3.13%)
occurrences (all)	1	1	1
Adverse drug reaction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Anxiety			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Depression			
subjects affected / exposed	0 / 7 (0.00%)	0 / 17 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 17 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Investigations			
Low density lipoprotein increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Transaminases increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 17 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	2
Injury, poisoning and procedural complications			
Skin abrasion			
subjects affected / exposed	1 / 7 (14.29%)	1 / 17 (5.88%)	1 / 32 (3.13%)
occurrences (all)	1	1	1
Electric shock			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Foot fracture			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	0 / 32 (0.00%)
occurrences (all)	0	1	0

Post-traumatic pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Limb injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 17 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Atrial fibrillation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 17 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	0 / 7 (0.00%)	0 / 17 (0.00%)	4 / 32 (12.50%)
occurrences (all)	0	0	6
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 7 (0.00%)	2 / 17 (11.76%)	2 / 32 (6.25%)
occurrences (all)	0	2	2
Vomiting			
subjects affected / exposed	0 / 7 (0.00%)	2 / 17 (11.76%)	0 / 32 (0.00%)
occurrences (all)	0	2	0
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Abdominal rigidity			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	0 / 32 (0.00%)
occurrences (all)	0	1	0

Constipation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 7 (0.00%)	0 / 17 (0.00%)	3 / 32 (9.38%)
occurrences (all)	0	0	3
Hepatobiliary disorders			
Hepatic cyst			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 7 (0.00%)	16 / 17 (94.12%)	4 / 32 (12.50%)
occurrences (all)	0	22	4
Hyperhidrosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Rash macular			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Rash pruritic			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Skin lesion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 17 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Renal cyst			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			

Gastroenteritis viral			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 17 (5.88%)	2 / 32 (6.25%)
occurrences (all)	0	1	2
COVID-19			
subjects affected / exposed	0 / 7 (0.00%)	0 / 17 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 7 (14.29%)	0 / 17 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 17 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Hypercholesterolaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 17 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Hyperlipidaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 17 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part B EYP001a 100mg	Part B EYP001a 200mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 31 (80.65%)	30 / 33 (90.91%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Adverse drug reaction			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Pain			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Anxiety			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Depression			
subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Insomnia			
subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	3	
Investigations			
Low density lipoprotein increased			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Transaminases increased			
subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	

Injury, poisoning and procedural complications			
Skin abrasion			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Electric shock			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Foot fracture			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Post-traumatic pain			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Limb injury			
subjects affected / exposed	0 / 31 (0.00%)	3 / 33 (9.09%)	
occurrences (all)	0	3	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Atrial fibrillation			
subjects affected / exposed	2 / 31 (6.45%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	3 / 31 (9.68%)	2 / 33 (6.06%)	
occurrences (all)	4	2	
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	0 / 31 (0.00%)	5 / 33 (15.15%)	
occurrences (all)	0	5	
Vomiting			
subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Abdominal pain			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	2	
Abdominal rigidity			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Diarrhoea			
subjects affected / exposed	1 / 31 (3.23%)	4 / 33 (12.12%)	
occurrences (all)	1	5	
Toothache			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Hepatobiliary disorders			
Hepatic cyst			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	19 / 31 (61.29%)	22 / 33 (66.67%)	
occurrences (all)	29	36	
Hyperhidrosis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Rash macular			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Rash pruritic			

subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Skin lesion			
subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Renal cyst			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Gastroenteritis viral			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Urinary tract infection			
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
COVID-19			
subjects affected / exposed	2 / 31 (6.45%)	1 / 33 (3.03%)	
occurrences (all)	2	2	
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	
occurrences (all)	0	0	
Type 2 diabetes mellitus			
subjects affected / exposed	2 / 31 (6.45%)	1 / 33 (3.03%)	
occurrences (all)	2	1	
Hypercholesterolaemia			
subjects affected / exposed	0 / 31 (0.00%)	3 / 33 (9.09%)	
occurrences (all)	0	4	
Hyperlipidaemia			
subjects affected / exposed	2 / 31 (6.45%)	0 / 33 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 November 2018	Consolidated and signed version of the draft sent to FDA
11 January 2019	Eligibility criteria restricted (reduced allowable variability in baseline ALT and AST). Version incorporating outcome of discussions with FDA during the IND review period.
28 May 2019	Eligibility criteria expanded (increased allowable variability in baseline ALT, AST, ALP, and total bilirubin). Increased Screening Period (increased from 60 days to 12 weeks). Centra lab reference ranges for ALT, AST, and ALP updated. Following correspondence on May 3, 2019 from ENYO to FDA regarding the high SF rate, and FDA's advice letter dated May 9, 2019 in which FDA provided recommended protocol modifications to improve the SF rate.
24 March 2020	Following DSMC-review of the unblinded Part A data and unscheduled interim analysis of Part A data (presented in Section 10), the following changes to study conduct were implemented: Eligibility criteria restricted: − Subjects with a BMI >45 kg/m2 were excluded. − eGFR exclusion criteria decreased from <60 mL/min/1.73 m2 to <50 mL/min/1.73 m2. Changes to study design: − Reduction in the number of subjects to be enrolled in Part B (reduced from 136 to 90 subjects). − Removal of the vonafexor 400 mg QD treatment group from Part B. − Dosing strategy for vonafexor a 200 mg QD in Part B updated to a step-up strategy (100 mg QD for the first 2 weeks of treatment, followed by an uptitration to 200 mg QD) to address the pruritus-related tolerance issues observed in the unblinded Part A data. − The Clinical Safety Monitoring Plan updated to ensure, in Part B, the DSMC were promptly notified for further review if any subjects experience ALT, AST, or bilirubin elevations 2×baseline values. − Removal of inhouse 24-hour PK monitoring.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported