Clinical trial results:
A Phase 2b Randomized, Double Blind, Placebo-Controlled, Multicenter Study Evaluating Safety and Efficacy of EDP-305 in Subjects with Liver-Biopsy Proven Non-Alcoholic Steatohepatitis (NASH) (ARGON-2)

Summary

EudraCT number	2019-003876-38
Trial protocol	DE GB
Global end of trial date	30 November 2021

Results information

Result version number	v1 (current)
This version publication date	05 January 2023
First version publication date	05 January 2023

Trial information

Trial identification

Sponsor protocol code	EDP305-102

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04378010
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Enanta Pharmaceuticals, Inc.
Sponsor organisation address	500 Arsenal St., Watertown, MA 02472, United States,
Public contact	Alaa Ahmad, Enanta Pharmaceuticals, Inc., 1 617-607-0800, aahmad@enanta.com
Scientific contact	Alaa Ahmad, Enanta Pharmaceuticals, Inc., 1 617-607-0800, aahmad@enanta.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	12 July 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 October 2021
Global end of trial reached?	Yes
Global end of trial date	30 November 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of EDP-305 compared to placebo on liver histology in non-cirrhotic NASH subjects with stage 2 or 3 fibrosis.
NOTE:
The pre-planned first interim analysis of a subjects through Week 12 provided meaningful information on dose selection and characterization for the compound. Enanta made a business decision to prioritize combination approaches for further development of the EDP-305. Therefore, this study on monotherapy was discontinued.

Protection of trial subjects:

Independent Ethics Committee or Institutional Review Board:
Written approval of the protocol, the final informed consent document, relevant supporting material and subject recruitment information was obtained from the independent ethics committee (IEC)/institutional review board (IRB) prior to study initiation.
Ethical Conduct of the Study:
This study was conducted in accordance with current applicable regulations, International Conference on Harmonisation (ICH) guidelines, and local legal requirements. It complies with the ethical principles described in the 18th World Medical Assembly (Helsinki 1964) and amendments of the 29th (Tokyo 1975), 35th (Venice 1983), the 41st (Hong Kong 1989) and the 48th (South Africa 1996) World Medical Assemblies, Declaration of Helsinki
Subject Information and Consent:
Informed consent was obtained from each subject before the subject was admitted to the study. The Investigator did not undertake any investigation specifically required for the clinical study until valid consent had been obtained. The terms of the consent and the date and time of day when it was obtained were documented in the case report form (CRF). The consent form, with the date and time of day when it was signed, was retained by the Investigator as part of the study records. A copy of the signed informed consent form (ICF) was given to the subject.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 January 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	United Kingdom: 3
Country: Number of subjects enrolled	United States: 92
Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Canada: 1
Worldwide total number of subjects	97
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)	76
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Male and female subjects with liver biopsy proven NASH between the ages of 18 and 75 years, inclusive, and with a NAS of 4 or greater with a score of at least 1 in each component of the NAS (steatosis scored 0-3, lobular inflammation scored 0-3, ballooning scored 0-2) and fibrosis stage 2 or 3 using the NASH (CRN) Histologic scoring system.

Pre-assignment

Screening details:

Screening assessments were to be conducted within 70 days prior to the first dose of study drug (i.e., Study Days -70 to -1). They were to be performed sequentially as follows: a) medical history and other noninvasive assessments, b) laboratory assessments, c) MRI-PDFF and MRE and, lastly, d) liver biopsy.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo orally for 72 weeks.
Matching placebo, which was identical in appearance to the test product except that it contained no active ingredient.

Arm type	Placebo
Investigational medicinal product name	Placebo EDP-305
Investigational medicinal product code	EDP-305
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Once a day orally for 72 weeks.

Arm title	EDP-305 1.5 mg

Arm description:

EDP-305 1.5 mg orally for 72 weeks (one 0.5 mg tablet and one 1.0 mg tablet).

Arm type	Experimental
Investigational medicinal product name	EDP-305 1.5 mg
Investigational medicinal product code	EDP-305
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral EDP-305 tablets, 1.5 mg administered once daily.

Arm title	EDP-305 2 mg

Arm description:

EDP-305 2.0 mg orally for 72 weeks (two 1.0 mg tablets).

Arm type	Experimental
Investigational medicinal product name	EDP-305 2 mg
Investigational medicinal product code	EDP-305
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral EDP-305 tablets, 2.0 mg administered once daily.

Number of subjects in period 1	Placebo	EDP-305 1.5 mg	EDP-305 2 mg
Started	32	32	33
Completed	32	32	33

Baseline characteristics

Reporting groups

Reporting group title	Overall Treatment Period

Reporting group description: -

Reporting group values	Overall Treatment Period	Total	
Number of subjects	97	97	
Age categorical 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)	0	0	
From 65-84 years	76	76	
85 years and over	21	21	
Gender categorical Units: Subjects			
Female	58	58	
Male	39	39	

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo orally for 72 weeks.
Matching placebo, which was identical in appearance to the test product except that it contained no active ingredient.

Reporting group title	EDP-305 1.5 mg

Reporting group description:

EDP-305 1.5 mg orally for 72 weeks (one 0.5 mg tablet and one 1.0 mg tablet).

Reporting group title	EDP-305 2 mg

Reporting group description:

EDP-305 2.0 mg orally for 72 weeks (two 1.0 mg tablets).

Primary: Proportion of subjects with ≥1 stage improvement in fibrosis without worsening of steatohepatitis and/or resolution of steatohepatitis and no worsening of liver fibrosis

End point title	Proportion of subjects with ≥1 stage improvement in fibrosis without worsening of steatohepatitis and/or resolution of steatohepatitis and no worsening of liver fibrosis[1]

End point description:

Proportion of subjects with ≥1 stage improvement in fibrosis without worsening of steatohepatitis and/or resolution of steatohepatitis and no worsening of liver fibrosis as determined by liver biopsy at Week 72.
NOTE:
99999: Due to study termination, the biopsy at Week 72 was not performed in any subject. Hence, there were no results to report. However, the system does not allow to keep the values blank. So, we have used "99999".

End point type	Primary

End point timeframe:

Screening to Week 72.

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: Due to study termination, the biopsy at Week 72 was not performed for any subject. Hence, there were no results to report and no statistical analysis was performed.

End point values	Placebo	EDP-305 1.5 mg	EDP-305 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	32	33	
Units: Number of Subjects	99999	99999	99999	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with improvement of fibrosis by at least 1 stage

and/or resolution of NASH without worsening of either

End point title	Proportion of subjects with improvement of fibrosis by at least 1 stage and/or resolution of NASH without worsening of either

End point description:

Proportion of subjects with improvement of fibrosis by at least 1 stage and/or resolution of NASH without worsening of either as determined by liver biopsy at Week 72.
NOTE:
Due to study termination, the biopsy at Week 72 was not performed for any subject. Hence, there were no results to report. However, the system does not allow to keep the values blank. So, we have used "99999".

End point type	Secondary

End point timeframe:

Screening to Week 72.

End point values	Placebo	EDP-305 1.5 mg	EDP-305 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	32	33	
Units: Number of Subjects	99999	99999	99999	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With no Worsening of Fibrosis Combined With no Worsening of NASH as Determined by Liver

End point title	Proportion of Subjects With no Worsening of Fibrosis Combined With no Worsening of NASH as Determined by Liver

End point description:

Proportion of Subjects With no Worsening of Fibrosis Combined With no Worsening of NASH as Determined by Liver.
NOTE:
Due to study termination, the biopsy at Week 72 was not performed for any subject. Hence, there were no results to report. However, the system does not allow to keep the values blank. So, we have used "99999".

End point type	Secondary

End point timeframe:

Screening to Week 72.

End point values	Placebo	EDP-305 1.5 mg	EDP-305 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	32	33	
Units: Number of Subjects	99999	99999	99999	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Resolution of Fibrosis

End point title	Proportion of Subjects With Resolution of Fibrosis

End point description:

Proportion of Subjects With Resolution of Fibrosis as Determined by Liver Biopsy at 72 Week.
NOTE:
Due to study termination, the biopsy at Week 72 was not performed for any subject. Hence, there were no results to report. However, the system does not allow to keep the values blank. So, we have used "99999".

End point type	Secondary

End point timeframe:

Screening to Week 72.

End point values	Placebo	EDP-305 1.5 mg	EDP-305 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	32	32	
Units: Number of Subjects	99999	99999	99999	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Improvement in Each Histologic Feature of NASH by at Least 1 Point

End point title	Proportion of Subjects With Improvement in Each Histologic Feature of NASH by at Least 1 Point

End point description:

Proportion of Subjects With Improvement in Each Histologic Feature of NASH by at Least 1 Point as determined by liver biopsy at Week 72.
NOTE:
Due to study termination, the biopsy at Week 72 was not performed for any subject. Hence, there were no results to report. However, the system does not allow to keep the values blank. So, we have used "99999".

End point type	Secondary

End point timeframe:

Screening to Week 72.

End point values	Placebo	EDP-305 1.5 mg	EDP-305 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	32	33	
Units: Number of Subjects	99999	99999	99999	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Improvement of Fibrosis by ≥ 2 Stages

End point title	Proportion of Subjects With Improvement of Fibrosis by ≥ 2 Stages

End point description:

Proportion of Subjects With Improvement of Fibrosis by ≥ 2 Stages by Liver Biopsy at Week 72.
NOTE:
Due to study termination, the biopsy at Week 72 was not performed for any subject. Hence, there were no results to report. However, the system does not allow to keep the values blank. So, we have used "99999".

End point type	Secondary

End point timeframe:

Screening to Week 72.

End point values	Placebo	EDP-305 1.5 mg	EDP-305 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	32	33	
Units: Number of Subjects	99999	99999	99999	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Improvement in NAS by at Least 2 Points With no Worsening of Fibrosis

End point title	Proportion of Subjects With Improvement in NAS by at Least 2 Points With no Worsening of Fibrosis

End point description:

Proportion of Subjects With Improvement in NAS by at Least 2 Points With no Worsening of Fibrosis as determined by liver biopsy at Week 72.
NOTE:
Due to study termination, the biopsy at Week 72 was not performed for any subject. Hence, there were no results to report. However, the system does not allow to keep the values blank. So, we have used "99999".

End point type	Secondary

End point timeframe:

Screening to Week 72.

End point values	Placebo	EDP-305 1.5 mg	EDP-305 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	32	33	
Units: Number of Subjects	99999	99999	99999	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Improvement of Fibrosis and Resolution of NASH

End point title	Proportion of Subjects With Improvement of Fibrosis and Resolution of NASH

End point description:

Proportion of Subjects With Improvement of Fibrosis and Resolution of NASH as a Composite Endpoint as defined by liver biopsy at Week 72.
NOTE:
Due to study termination, the biopsy at Week 72 was not performed for any subject. Hence, there were no results to report. However, the system does not allow to keep the values blank. So, we have used "99999".

End point type	Secondary

End point timeframe:

Screening to Week 72.

End point values	Placebo	EDP-305 1.5 mg	EDP-305 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	32	33	
Units: Number of Subjects	99999	99999	99999	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Resolution of NASH and no Worsening of Liver Fibrosis

End point title	Proportion of Subjects With Resolution of NASH and no Worsening of Liver Fibrosis

End point description:

Proportion of Subjects With Resolution of NASH and no Worsening of Liver Fibrosis.
NOTE:
Due to study termination, the biopsy at Week 72 was not performed for any subject. Hence, there were no results to report. However, the system does not allow to keep the values blank. So, we have used

"99999".

End point type	Secondary

End point timeframe:

Screening to Week 72.

End point values	Placebo	EDP-305 1.5 mg	EDP-305 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	32	33	
Units: Number of Subjects	99999	99999	99999	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Histological Progression to Cirrhosis as determined by Liver Biopsy

End point title	Proportion of Subjects With Histological Progression to Cirrhosis as determined by Liver Biopsy

End point description:

Proportion of Subjects With Histological Progression to Cirrhosis as determined by Liver Biopsy at Week 72.
NOTE:
Due to study termination, the biopsy at Week 72 was not performed for any subject. Hence, there were no results to report. However, the system does not allow to keep the values blank. So, we have used "99999".

End point type	Secondary

End point timeframe:

Screening to Week 72.

End point values	Placebo	EDP-305 1.5 mg	EDP-305 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	32	33	
Units: Number of Subjects	99999	99999	99999	

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of TEAEs Leading to Discontinuation

End point title	Frequency of TEAEs Leading to Discontinuation

End point description:

Frequency of TEAEs Leading to discontinuation.

End point type	Secondary

End point timeframe:

From time of informed consent through Week 72 and 4-week follow-up period.

End point values	Placebo	EDP-305 1.5 mg	EDP-305 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	32	33	
Units: Number of Subjects	4	8	14	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change of Fat in the Liver From Baseline Versus Placebo

End point title	Percentage Change of Fat in the Liver From Baseline Versus Placebo

End point description:

Percentage Change of Fat in the Liver From Baseline Versus Placebo.

End point type	Secondary

End point timeframe:

Baseline to Week 12.

End point values	Placebo	EDP-305 1.5 mg	EDP-305 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	24	17	
Units: percent				
number (confidence interval 95%)	0 (0 to 0)	-11.261 (-24.723 to 2.200)	-11.718 (-26.342 to 2.906)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Liver Stiffness From Baseline Versus Placebo

End point title	Change in Liver Stiffness From Baseline Versus Placebo

End point description:

Change in Liver Stiffness From Baseline Versus Placebo.

End point type	Secondary

End point timeframe:

Baseline to Week 12.

End point values	Placebo	EDP-305 1.5 mg	EDP-305 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	24	17	
Units: KPa				
least squares mean (confidence interval 95%)	0 (0 to 0)	0.591 (-0.035 to 1.216)	1.050 (0.365 to 1.736)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in 5D-itch Scale From Baseline

End point title	Change in 5D-itch Scale From Baseline

End point description:

Change in 5D-itch Scale From Baseline.

End point type	Secondary

End point timeframe:

Baseline to Week 12.

End point values	Placebo	EDP-305 1.5 mg	EDP-305 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	7	6	
Units: Score				
least squares mean (confidence interval 95%)	0 (0 to 0)	-0.439 (-5.458 to 4.579)	1.880 (-3.479 to 7.239)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Triglycerides From Baseline

End point title	Change in Triglycerides From Baseline

End point description:

Change in Triglycerides From Baseline.

End point type	Secondary

End point timeframe:
Baseline to Week 12.

End point values	Placebo	EDP-305 1.5 mg	EDP-305 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	28	26	
Units: mmol/L				
arithmetic mean (standard deviation)	-0.06 (± 0.752)	-0.16 (± 0.725)	-0.14 (± 0.839)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Adiponectin From Baseline

End point title	Change in Adiponectin From Baseline

End point description:
Change in Adiponectin From Baseline.

End point type	Secondary

End point timeframe:
Baseline through Week 12.

End point values	Placebo	EDP-305 1.5 mg	EDP-305 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	27	24	
Units: µg/L				
arithmetic mean (standard deviation)	228.27 (± 866.829)	330.25 (± 1309.414)	-85.44 (± 1199.182)	

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of EDP-305

End point title	Plasma Concentration of EDP-305[2]

End point description:

End point type	Secondary

End point timeframe:
Baseline through Week 12.

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: The Placebo arm did not take part in the determination of plasma concentration. So, we have excluded it.

End point values	EDP-305 1.5 mg	EDP-305 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	7		
Units: ng/mL				
arithmetic mean (standard deviation)	17.3783 (± 15.13460)	30.0286 (± 24.07237)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in VAS (Visual Analog Score) From Baseline

End point title	Change in VAS (Visual Analog Score) From Baseline

End point description:

End point type	Secondary

End point timeframe:

Baseline to Week 12.

End point values	Placebo	EDP-305 1.5 mg	EDP-305 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	28	25	
Units: Score				
least squares mean (confidence interval 95%)	0 (0 to 0)	7.211 (-4.997 to 19.418)	12.986 (0.608 to 25.363)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Total Cholesterol From Baseline

End point title	Change in Total Cholesterol From Baseline

End point description:

Change in Total Cholesterol From Baseline.

End point type	Secondary

End point timeframe:

Baseline to Week 12.

End point values	Placebo	EDP-305 1.5 mg	EDP-305 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	28	26	
Units: mmol/L				
arithmetic mean (standard deviation)	0 (± 0.946)	0.07 (± 0.977)	-0.07 (± 1.116)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in HDL From Baseline

End point title	Change in HDL From Baseline
End point description: Change in HDL From Baseline.	
End point type	Secondary
End point timeframe: Baseline to Week 12.	

End point values	Placebo	EDP-305 1.5 mg	EDP-305 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	27	25	
Units: mmol/L				
arithmetic mean (standard deviation)	0.01 (± 0.149)	-0.08 (± 0.200)	-0.11 (± 0.255)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in LDL From Baseline

End point title	Change in LDL From Baseline
End point description: Change in LDL From Baseline.	
End point type	Secondary
End point timeframe: Baseline to Week 12.	

End point values	Placebo	EDP-305 1.5 mg	EDP-305 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	28	26	
Units: mmol/L				
arithmetic mean (standard deviation)	-0.03 (± 0.835)	0.24 (± 0.856)	0.08 (± 0.949)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Day 1 to Week 72.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1
Reporting groups	
Reporting group title	Placebo
Reporting group description: Once a day tablet orally for 72 weeks.	
Reporting group title	EDP-305 1.5 mg
Reporting group description: Once a day orally for 72 weeks. EDP-305 1.5 mg: Tablet.	
Reporting group title	EDP-305 2 mg
Reporting group description: Once a day orally for 72 weeks. EDP-305 2 mg: Tablet.	

Serious adverse events	Placebo	EDP-305 1.5 mg	EDP-305 2 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	0 / 33 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	0 / 33 (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
Pancreatitis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	0 / 33 (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

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

Non-serious adverse events	Placebo	EDP-305 1.5 mg	EDP-305 2 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 32 (62.50%)	28 / 32 (87.50%)	31 / 33 (93.94%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	1 / 33 (3.03%)
occurrences (all)	0	2	1
Blood pressure increased			
subjects affected / exposed	2 / 32 (6.25%)	0 / 32 (0.00%)	0 / 33 (0.00%)
occurrences (all)	2	0	0
Lipase increased			
subjects affected / exposed	2 / 32 (6.25%)	0 / 32 (0.00%)	2 / 33 (6.06%)
occurrences (all)	3	0	3
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	2 / 32 (6.25%)	0 / 32 (0.00%)	0 / 33 (0.00%)
occurrences (all)	2	0	0
Post vaccination syndrome			
subjects affected / exposed	2 / 32 (6.25%)	0 / 32 (0.00%)	0 / 33 (0.00%)
occurrences (all)	4	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 32 (3.13%)	1 / 32 (3.13%)	2 / 33 (6.06%)
occurrences (all)	1	1	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 32 (3.13%)	2 / 32 (6.25%)	3 / 33 (9.09%)
occurrences (all)	1	2	3
Headache			
subjects affected / exposed	2 / 32 (6.25%)	2 / 32 (6.25%)	3 / 33 (9.09%)
occurrences (all)	2	2	3
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	3 / 33 (9.09%)
occurrences (all)	0	2	3
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 32 (3.13%)	3 / 32 (9.38%)	1 / 33 (3.03%)
occurrences (all)	1	4	1
Abdominal pain lower			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	1 / 33 (3.03%)
occurrences (all)	0	3	1
Abdominal pain upper			
subjects affected / exposed	1 / 32 (3.13%)	2 / 32 (6.25%)	4 / 33 (12.12%)
occurrences (all)	1	3	6
Diarrhoea			
subjects affected / exposed	3 / 32 (9.38%)	1 / 32 (3.13%)	2 / 33 (6.06%)
occurrences (all)	3	1	2
Nausea			
subjects affected / exposed	3 / 32 (9.38%)	2 / 32 (6.25%)	1 / 33 (3.03%)
occurrences (all)	3	2	1
Toothache			
subjects affected / exposed	2 / 32 (6.25%)	0 / 32 (0.00%)	0 / 33 (0.00%)
occurrences (all)	2	0	0
Vomiting			
subjects affected / exposed	2 / 32 (6.25%)	1 / 32 (3.13%)	1 / 33 (3.03%)
occurrences (all)	3	1	1
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	2 / 32 (6.25%)	0 / 32 (0.00%)	0 / 33 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	12 / 32 (37.50%)	25 / 32 (78.13%)	25 / 33 (75.76%)
occurrences (all)	21	63	65
Rash			
subjects affected / exposed	1 / 32 (3.13%)	3 / 32 (9.38%)	2 / 33 (6.06%)
occurrences (all)	1	4	2
Urticaria			
subjects affected / exposed	0 / 32 (0.00%)	0 / 32 (0.00%)	2 / 33 (6.06%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	2 / 32 (6.25%)	1 / 32 (3.13%)	0 / 33 (0.00%)
occurrences (all)	2	1	0
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 32 (3.13%)	3 / 32 (9.38%)	1 / 33 (3.03%)
occurrences (all)	1	3	1
Urinary tract infection			
subjects affected / exposed	4 / 32 (12.50%)	4 / 32 (12.50%)	3 / 33 (9.09%)
occurrences (all)	4	6	8
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 32 (6.25%)	0 / 32 (0.00%)	1 / 33 (3.03%)
occurrences (all)	2	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 May 2020	• Inclusion criterion 11 was updated to make clear that the intention was that antihypertensive subjects would be on a stable antihypertensive regimen during the study. • The following exclusion criteria were revised to the text as given in the CSR to capture the target subject population: exclusion criteria 5, 9, 12, 13, 14, 17, 19, 20, 25, 26. Text in other parts of the CSP were updated as appropriate to reflect changes in the exclusion criteria. • Additional information on concomitant medications was added as follows: Generic substitutions of all stable medications for underlying diseases were allowed during the study. Changing a medication within the same therapeutic class was also permitted during the study. Any subject who initiated a high dose or increased to a higher dose of Vitamin E (≥800 IU/day) during the course of the study had to undergo ET procedures (including liver biopsy and imaging if beyond Week 36). • Changes were made to update the NCI CTCAE version and provide clarification around documenting and reporting of AEs. • At home pregnancy tests were added at Weeks 52, 60, and 68 for females of childbearing potential. Due to the 8-week timeframe between clinic visits at Weeks 48, 56, and 72, these at home pregnancy tests were added to confirm subjects did not become pregnant during the extended time between visits. To determine the results of the pregnancy tests, additional phone contacts were added • The number of laboratory tests conducted to assess lipids and cardiovascular risk were reduced. These were no longer deemed necessary based on data readouts from previous studies.
21 March 2021	The screening time was extended from 8 to 10 weeks because additional time was needed to allow more flexibility for completion of all screening procedures in a sequential manner • The inclusion criteria for MRI-PDFF ≥8% and AST >30 IU/L were added to further refine the subject population eligible for study entry and thus increase the probability of resulting in eligible liver biopsy criteria • To avoid unnecessary burden on potential subjects, the inclusion criteria were modified to specify that screening assessments should be performed in a sequential manner and the liver biopsy should only be performed once the subject satisfied all other eligibility criteria • To avoid confusion noted by the sites with regard to the duration of a month (i.e., 28, 30, or 31 days), durations were changed from months to corresponding weeks throughout the CSP • Wording on Screening and use of concomitant medications was clarified with regard to rescreening options for subjects who required a medically necessary dose modification with an existing medication • The schedule of assessments was modified so that for subjects who discontinued between Weeks 10 and 12, the MRI/MRE that would have been conducted at Week 12 was to be conducted at the EOT visit • The wording of ECG requirements was revised to clarify ECG repeat requirements because the original language was proving to be confusing to sites. Normal ranges for ECG assessments were provided. • Due to the COVID 19 pandemic, provisions were added to clarify options for rescreening subjects who were affected by COVID 19 • Wording regarding the reporting of AEs was revised to simplify the recording requirements for AEs and all AEs collected would be entered into the eCRF • Clarified that DLQI was only to be completed at each in-clinic visit as opposed to all visits • The wording was revised to emphasize the need for reviewing eligibility criteria and detailing the definition of women childbearing potential.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
04 October 2021	Enanta Pharmaceuticals, Inc. made the strategic decision to discontinue the ARGON-2 study to prioritize combination treatment approaches. This decision was not based on safety concerns.	-

Notes:

Limitations and caveats

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

No limitations reported for the study.

Notes: