Clinical trial results:
A Multicenter, Open Label, Single- and Multiple-Dose, Dose Finding Study to Assess the Effects of Obeticholic Acid in Pediatric Subjects with Biliary Atresia

Summary

EudraCT number	2014-004693-42
Trial protocol	GB DE NL BE FI FR PL ES IT
Global end of trial date	09 March 2023

Results information

Result version number	v2 (current)
This version publication date	30 May 2024
First version publication date	24 September 2023
Version creation reason	• Correction of full data set correct errors

Trial information

Trial identification

Sponsor protocol code	747-206

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05321524
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Intercept Pharmaceuticals, Inc.
Sponsor organisation address	305 Madison Avenue, Morristown, New Jersey, United States, 07960
Public contact	Intercept Pharmaceuticals, Inc., Intercept Pharmaceuticals, Inc., +1 844 782-4278, medinfo@interceptpharma.com
Scientific contact	Medical Information, Medical Information, +1 844 782-4278, medinfo@interceptpharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001304-PIP02-13
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	09 March 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 March 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

- Safety and tolerability
- Pharmacokinetics (PK) of Obeticholic acid (OCA) and its conjugates
  - o Single dose (SD) Phase: To assess the PK of low dose OCA and its conjugates and to determine the appropriate dose of OCA in the multiple dose (MD) Phase
  - o MD Phase: To assess the PK of a range of OCA doses and its conjugates after a single dose and at steady state

Protection of trial subjects:

The study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the Sponsor's policies.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2015
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	Belgium: 4
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Germany: 3
Worldwide total number of subjects	8
EEA total number of subjects	7

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)	4
Adolescents (12-17 years)	4

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was an open label, SD and MD, dose-finding study that evaluated the safety, tolerability, PK, and pharmacodynamics (PD) of a range of OCA doses pediatric participants with biliary atresia with successful hepatoportoenterostomy (HPE).

Pre-assignment

Screening details:

A total of 8 participants were enrolled from 3 countries (Belgium, Germany, and the United Kingdom).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	SD MD Control Low Dose Cohort

Arm description:

Participants entered the OLE phase and continued to receive OCA from the SD MD phase for up to 2 years to assess the effects of long-term OCA treatment.

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

Dosage and administration details:

Participants were treated with adult equivalent OCA doses based on body weight..

Arm title	SD MD Low Dose Cohort

Arm description:

Participants entered OLE phase and received SD MD low dose of OCA.

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

Dosage and administration details:

Subjects were treated with adult equivalent OCA doses of 1.5 milligrams (mg), 5 mg, and 10 mg daily (Low, Medium, or High OCA dose cohorts, respectively) based on body weight.

Number of subjects in period 1	SD MD Control Low Dose Cohort	SD MD Low Dose Cohort
Started	1	7
Completed	0	0
Not completed	1	7
Physician decision	1	1
Sponsor decision due to elevated PK profiles	-	1
Confirmed Elevated Lipase	-	1
Non-compliance with study drug	-	1
Study terminated by sponsor	-	2
Interruption of the IP supply from the sponsor	-	1

Baseline characteristics

Reporting groups	
Reporting group title	SD MD Control Low Dose Cohort
Reporting group description:	
Participants entered the OLE phase and continued to receive OCA from the SD MD phase for up to 2 years to assess the effects of long-term OCA treatment.	
Reporting group title	SD MD Low Dose Cohort
Reporting group description:	
Participants entered OLE phase and received SD MD low dose of OCA.	

Reporting group values	SD MD Control Low Dose Cohort	SD MD Low Dose Cohort	Total
Number of subjects	1	7	8
Age categorical Units: Subjects			
Children (2-11 years)	0	4	4
Adolescents (12-17 years)	1	3	4
Gender categorical Units: Subjects			
Female	1	6	7
Male	0	1	1

End points

End points reporting groups

Reporting group title	SD MD Control Low Dose Cohort
Reporting group description:	
Participants entered the OLE phase and continued to receive OCA from the SD MD phase for up to 2 years to assess the effects of long-term OCA treatment.	
Reporting group title	SD MD Low Dose Cohort
Reporting group description:	
Participants entered OLE phase and received SD MD low dose of OCA.	

Primary: Number of participants reporting serious treatment emergent adverse events (serious TEAEs) and non-serious TEAEs

End point title	Number of participants reporting serious treatment emergent adverse events (serious TEAEs) and non-serious TEAEs[1]
End point description:	
An adverse event (AE) is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. Treatment-emergent adverse events/treatment-emergent serious adverse events (TEAEs/TESAEs) are defined as any event that began or worsened in severity on or after the first dose of study drug.	
End point type	Primary
End point timeframe:	
Up to 17 Weeks	

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: The statistical analyses were not executed as pre-specified as the study was early terminated.

End point values	SD MD Control Low Dose Cohort	SD MD Low Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	7		
Units: Count of participants				
number (not applicable)				
Any serious TEAE	0	2		
Any non-serious TEAE	0	7		

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with clinically significant changes in electrocardiogram (ECG), physical exam, clinical laboratory results, and vital signs.

End point title	Number of participants with clinically significant changes in electrocardiogram (ECG), physical exam, clinical laboratory results, and vital signs.[2]

End point description:

Blood samples were planned to be collected for the analysis of clinically significant changes in ECG, physical exam, clinical laboratory results, and vital signs. 99999 indicates that the study was terminated after extensive efforts to improve recruitment and it was not feasible to enroll the requisite number of participants to generate data needed to meet the study objectives. European Medicine Agency (EMA) Paediatric Committee agreed with the Sponsor to terminate the study.

End point type	Primary

End point timeframe:

Up to 17 Weeks

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analyses were not executed as pre-specified as the study was early terminated.

End point values	SD MD Control Low Dose Cohort	SD MD Low Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	7		
Units: Count of participants				
number (not applicable)	99999	99999		

Statistical analyses

No statistical analyses for this end point

Primary: Plasma concentrations of OCA

End point title	Plasma concentrations of OCA[3]

End point description:

Blood samples were planned to be collected for the analysis of plasma concentrations of OCA. 99999 indicates that the study was terminated after extensive efforts to improve recruitment and it was not feasible to enroll the requisite number of participants to generate data needed to meet the study objectives. EMA Paediatric Committee agreed with the Sponsor to terminate the study.

End point type	Primary

End point timeframe:

Up to Day 63

Notes:

[3] - 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: The statistical analyses were not executed as pre-specified as the study was early terminated.

End point values	SD MD Control Low Dose Cohort	SD MD Low Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	7		
Units: Picograms per milliliter				
geometric mean (geometric coefficient of variation)	99999 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with clinically significant changes in clinical chemistry

End point title	Number of participants with clinically significant changes in clinical chemistry

End point description:

Blood samples were planned to be collected at indicated timepoints for the analysis of clinical chemistry parameters including alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and total and direct (conjugated) bilirubin. 99999 indicates that the study was terminated after extensive efforts to improve recruitment and it was not feasible to enroll the requisite number of participants to generate data needed to meet the study objectives. EMA Paediatric Committee agreed with the Sponsor to terminate the study.

End point type	Secondary

End point timeframe:

Up to 17 Weeks

End point values	SD MD Control Low Dose Cohort	SD MD Low Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	7		
Units: Count of participants				
number (not applicable)	99999	99999		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentrations of C4

End point title	Plasma concentrations of C4

End point description:

Serum samples were planned to be collected for the analysis of plasma concentrations of C 24. 99999 indicates that the study was terminated after extensive efforts to improve recruitment and it was not feasible to enroll the requisite number of participants to generate data needed to meet the study objectives. EMA Paediatric Committee agreed with the Sponsor to terminate the study.

End point type	Secondary

End point timeframe:

Up to Day 63

End point values	SD MD Control Low Dose Cohort	SD MD Low Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	7		
Units: nanogram per milliliter				
least squares mean (standard deviation)	99999 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentrations of bile acids

End point title	Plasma concentrations of bile acids

End point description:

Serum samples were planned to be collected for the analysis of plasma concentrations of bile acids. 99999 indicates that the study was terminated after extensive efforts to improve recruitment and it was not feasible to enroll the requisite number of participants to generate data needed to meet the study objectives. EMA Paediatric Committee agreed with the Sponsor to terminate the study.

End point type	Secondary

End point timeframe:

Up to Day 63

End point values	SD MD Control Low Dose Cohort	SD MD Low Dose Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	7		
Units: nanomoles*gram per liter				
least squares mean (standard deviation)	99999 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 17 Weeks

Adverse event reporting additional description:

Treatment emergent adverse events and serious treatment adverse events were collected in Safety Population. Safety population included all participants who received OCA with their current standard of care treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25

Reporting groups

Reporting group title	SD MD Low Dose Cohort

Reporting group description:

Subjects received SD MD low dose of OCA.

Reporting group title	SD MD Control Low Dose Cohort

Reporting group description:

Participants continued to receive OCA from the SD MD phase.

Serious adverse events	SD MD Low Dose Cohort	SD MD Control Low Dose Cohort	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 7 (28.57%)	0 / 1 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
Pneumococcal sepsis			

subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	SD MD Low Dose Cohort	SD MD Control Low Dose Cohort	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	0 / 1 (0.00%)	
Vascular disorders			
Pallor			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 7 (28.57%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Pyrexia			
subjects affected / exposed	2 / 7 (28.57%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Wheezing			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Depressive symptom			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Selective mutism			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Investigations			

Blood bilirubin increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Lipase increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Urine albumin/creatinine ratio increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Traumatic haematoma			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 7 (42.86%)	0 / 1 (0.00%)	
occurrences (all)	4	0	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Lymphopenia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Neutropenia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Splenomegaly			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Ocular hyperaemia			

subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 7 (28.57%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Varices oesophageal			
subjects affected / exposed	2 / 7 (28.57%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Portal hypertensive enteropathy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Portal hypertensive gastropathy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hepatosplenomegaly			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Dry skin			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Eczema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 7 (42.86%)	0 / 1 (0.00%)	
occurrences (all)	6	0	
Bronchitis			
subjects affected / exposed	2 / 7 (28.57%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Hordeolum			

subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Lice infestation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Otitis media			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Pneumococcal sepsis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Pyelonephritis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Vitamin A deficiency			
subjects affected / exposed	1 / 7 (14.29%)	0 / 1 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 April 2015	The protocol has been amended to implement an open label extension (OLE).
17 June 2015	Based on feedback from regulatory authorities, the stopping criteria and subsequent regulatory action has been clarified and defined.
17 July 2015	Based on feedback from regulatory authorities, acceptable methods of contraception have been clarified and defined. Additionally, exclusion criteria for females of child-bearing potential has been added.
07 September 2015	Protocol 2 has been prepared to: Change the terminology of the OCA drug formulation that will be used for the younger and smaller children from "oral suspension" to "pediatric formulation" since an oral suspension will not be used. The pediatric formulation is currently under development and therefore a generic term is more appropriate at this time; Clarify the timing and process for initiating enrollment of the younger group of children (<2 years); Clarify that standard of care medications for the treatment of biliary atresia (eg, UDCA) need to be stable for at least 1 month prior to Day 1; Clarify that the collection of a blood sample is intended for all participants at each visit per Table 1 and Table 2 who meet the minimum enrollment weight restriction on Day 0 of ≥20 kilograms (kg). Initially, the protocol indicated that blood would only be drawn for participants who weighed ≥20 kg at the time of each visit. participants who have slight weight loss resulting in a weight <20 kg should still provide a blood sample at each respective visit. Originally, the minimum weight requirement was defined based on the ability to dose the participants appropriately without having a pediatric formulation available, and was not based on any safety concerns for participants who weighed <20 kg; Updated the Table of Procedures (Table 2 and Table 3) for the OLE phase to include the procedures required for participants who enroll into the OLE phase at a time other than the end of the SD MD phase (Day 64); Clarify that participants who enroll in the OLE phase ≥3 weeks to ≤3 months and >3 months will be dispensed OCA on Day 1, but will be instructed to wait for a telephone contact by the principle investigator (PI) or designee before starting dosing; Clarify in the Procedure Section the list of procedures required for participants who enroll in the OLE phase at a time other than the end of the SD MD phase (Day 64); Delete dose charts in Appendix B as it is not necessary to include.
18 April 2016	OCA 0.1 mg mini-tablet formulation has become available for dosing of participants aged <2 years. Protocol Version 3 includes details regarding this formulation and dosing instructions. Further, the weight restrictions on participant enrollment have been clarified. Other major changes include addition of exploratory objectives: (1) accessibility and swallowability and (2) palatability.

07 April 2017	The pathophysiology of biliary atresia is known to include portal hypertension, cholestasis, and/or hepatic impairment (cirrhosis). The presence and magnitude of these disease features are likely to have a substantial impact on the plasma and/or liver concentrations of OCA. Although there are no safety concerns, as a precautionary measure, additional time has been added to receive single-dose pharmacokinetics (PK) data for all participants being treated with OCA prior to the start of the MD phase. This additional time is intended to allow for a decision regarding whether each participant should proceed into the MD phase or be discontinued from the study. Exclusion criteria for participants with aspartate aminotransferase (AST) to platelet ratio index Aspartate aminotransferase to platelet ratio index (APRI) >0.95 was added to make sure participants are unnecessarily exposed to high levels of OCA. Participants would be allowed to rescreen. Based on PK data from the initial participants enrolled into the low dose arm of this protocol, which showed a positive relationship between single-dose total OCA area under the concentration-time curve from time 0 to 24 hours (AUC0-24h) exposure and the APRI calculated at the screening visit, APRI will also be used as a preliminary predictor of exposure. Visit window extensions for Days 7 and 14 have been incorporated to receive and evaluate single-dose PK data for participants prior to entering the MD phase due to disease features (ie, portal hypertension) playing a significant role in OCA PK exposure. Additional visits have been added for Control participants enrolling into the OLE, to evaluate baseline characteristics prior to assigning participants to an appropriate dose group.
18 December 2017	There are not known or accepted clinical parameters to evaluate the efficacy of therapies such as OCA in participants with post-hepatoportoenterostomy (HPE) biliary atresia. There is a mechanistic rationale for OCA as a candidate for the treatment of post-HPE biliary atresia based on its farnesoid X receptor (FXR) mediated hepatoprotective properties including improvement in choleresis, inhibition of the progression to fibrosis, reversal of established fibrosis, and the ability of OCA to counteract hepatic inflammation. Modifications have been made to transition the intent of the 747-206 trial from proof of concept to a clinical pharmacology and proof of mechanism study that assesses safety, PK, and pharmacodynamics (PD). Efficacy will be evaluated in subsequent studies. Additionally, based on participant PK data received to date, there has been difficulty in predicting OCA exposure due to varying levels of disease manifestations, including portal hypertension, and therefore OCA exposure has shown to be higher than anticipated in certain participants. No adverse events or safety concerns existed with the higher exposures seen, in fact some measurements of transaminases improved with OCA dosing. However, this finding required a re-assessment of the study design to minimize the potential risk of high OCA exposure.
25 January 2019	Previous iterations of the study protocol allowed the use of contraceptives that did not meet the criteria of a failure rate of less than 1% per year. The current protocol revision updates the entry criteria to limit the acceptable methods of contraceptives to be compliant with a failure rate of less than 1% per year. Additionally, protocol version 5 lacked clarity on the combination of tablets to achieve the most appropriate weight adjusted dose. The current protocol revision includes dosing charts describing the combination of tablets to achieve the most accurate target dose as well as an alternate dose minimizing the number of tablets while remaining accurate to maximize participant compliance.
06 May 2021	The three most important modifications to the protocol include a reduction of the sample size by elimination of several dose cohorts in both the Single-Dose (SD) and Multiple-Dose (MD) Phases, a reduction in the duration of the MD Phase from 8 to 4 weeks, and a reintroduction of an OLE Phase following the MD Phase. Other changes include updating the Introduction, including the literature review and clinical history with OCA, changing the eligibility criteria (inclusion and exclusion criteria) to enroll more stable participants, and updating the Drug-induced Liver Injury (DILI) Algorithm and safety tables according to advisory board suggestions.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
09 March 2023	Justifications: After extensive efforts by the sponsor to improve study recruitment, including obtaining EMA scientific advise, holding advisory board with key opinion leaders, and executing seven protocol amendments, it is deemed not feasible to enroll the requisite number of subjects for this study to generate the data needed to meet the study objectives. As a result of this determination, in agreement with the EMA Paediatric Committee, the sponsor has decided to terminate study 747-206.	-

Notes:

Limitations and caveats

None reported