Clinical trial results:
Pharmacokinetics of Cobitolimod Enemas in Participants with active Ulcerative Colitis

Summary

EudraCT number	2021-003023-14
Trial protocol	SE
Global end of trial date	19 January 2023

Results information

Result version number	v1 (current)
This version publication date	22 November 2023
First version publication date	22 November 2023

Trial information

Trial identification

Sponsor protocol code	CSUC-02/21

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05404074
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	InDex Pharmaceuticals AB
Sponsor organisation address	Berzelius väg 13, Solna, Sweden, 171 65
Public contact	Eva Arlander, Chief Development Officer, InDex Pharmaceuticals AB, +46 (0)8 122 038 70, eva.arlander@indexpharma.com
Scientific contact	Eva Arlander, Chief Development Officer, InDex Pharmaceuticals AB, +46 (0)8 122 038 70, eva.arlander@indexpharma.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	19 January 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 January 2023
Global end of trial reached?	Yes
Global end of trial date	19 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess PK properties of cobitolimod in plasma after administration of cobitolimod enema in participants with active UC and in remission.

Protection of trial subjects:

The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are compliant with the International Conference of Harmonisation (ICH) Good Clinical Practice (GCP) E6 (R2) guidance, the European Union (EU) Clinical Trials Directive 2001/20/EC, and applicable local regulatory requirements.
It was the responsibility of the Investigator or an authorised associate to give each potential study participant adequate verbal and written information before any study specific assessments were performed.
The information included the objectives and the procedures of the study as well as any risks or inconvenience involved. It was emphasised that participation in the study was voluntary, and that the participant could withdraw from participation at any time and for any reason, without any prejudice. All participants were given the opportunity to ask questions about the study and were given sufficient time to consider participation before signing the Informed consent form (ICF).
Before performing any study-related procedures, the ICF was signed and personally dated by the participant and by the Investigator. A copy of the participant information including the signed ICF was provided to the participant.
Documentation of the discussion and the date of informed consent were recorded in the source documentation and in the electronic case report form (eCRF). The participant information sheet and the signed ICF were filed by the Investigator for possible future audits and/or inspections.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 November 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 8
Worldwide total number of subjects	8
EEA total number of subjects	8

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)	7
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The participants were identified by referring participating physicians or recruited from advertising in media (including social media) or recruited from the CTC's database of study participants and from the Uppsala University Hospital catchment area.

Pre-assignment

Screening details:

In total, 12 participants were screened, and 8 participants were included and dosed in the study (Full analysis set). Seven (7) participants completed the study according to protocol (PK analysis set) and of those, 4 participants were in clinical remission after the second dose and therefore received a third dose cobitolimod.

Period 1

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

Arms

Arm title	Total

Arm description:

All 8 participants included and dosed in the study.

Arm type	Experimental
Investigational medicinal product name	Cobitolimod 500 mg
Investigational medicinal product code	
Other name	Kappaproct
Pharmaceutical forms	Rectal solution
Routes of administration	Rectal use

Dosage and administration details:

Rectal administration. Participants self-administered a single rectal enema at Visit 2, 3 and, if the participants were in remission, at Visit 4.

Number of subjects in period 1	Total
Started	8
Completed	8

Baseline characteristics

Reporting groups	
Reporting group title	Total
Reporting group description:	
All 8 participants included and dosed in the study.	

Reporting group values	Total	Total	
Number of subjects	8	8	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	45.8		
standard deviation	± 18.7	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	4	4	

Subject analysis sets	
Subject analysis set title	Remitters
Subject analysis set type	Per protocol
Subject analysis set description:	
This analysis set summarizes data for participants in remission (remitters).	
Subject analysis set title	Non-remitters
Subject analysis set type	Per protocol
Subject analysis set description:	
This analysis set summarizes data for participants not in remission (non-remitters)	

Reporting group values	Remitters	Non-remitters	
Number of subjects	4	4	
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			

Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	40.8	50.8	
standard deviation	± 11.7	± 24.7	
Gender categorical Units: Subjects			
Female	2	2	
Male	2	2	

End points

End points reporting groups

Reporting group title	Total
Reporting group description:	
All 8 participants included and dosed in the study.	
Subject analysis set title	Remitters
Subject analysis set type	Per protocol
Subject analysis set description:	
This analysis set summarizes data for participants in remission (remitters).	
Subject analysis set title	Non-remitters
Subject analysis set type	Per protocol
Subject analysis set description:	
This analysis set summarizes data for participants not in remission (non-remitters)	

Primary: Maximum Observed Plasma Concentrations (Cmax)

End point title	Maximum Observed Plasma Concentrations (Cmax)[1]
End point description:	
Venous blood samples (approximately 5 mL) for the determination of plasma concentrations of cobitolimod after administration of the study intervention, were collected through an indwelling venous catheter. At Visit 4b, only the remitters were included.	
End point type	Primary
End point timeframe:	
Week 0 (Visit 2) and Week 6 (Visit 4b, remitters only)	

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: Per protocol, the end-point is reported using descriptive statistics only.

End point values	Remitters	Non-remitters		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4[2]	3[3]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Visit 2	42.97 (± 132)	25.28 (± 52.3)		
Visit 4b	13.34 (± 72.7)	0 (± 0)		

Notes:

[2] - PK analysis set.

[3] - PK analysis set. Visit 4b = 0 subjects

Statistical analyses

No statistical analyses for this end point

Primary: Time to Cmax (Tmax)

End point title	Time to Cmax (Tmax)[4]
End point description:	
Measure Description Venous blood samples (approximately 5 mL) for the determination of plasma	

concentrations of cobitolimod after administration of the study intervention, were collected through an indwelling venous catheter.

At Visit 4b (Week 6), only the remitters were included.

End point type	Primary

End point timeframe:

Week 0 (Visit 2) and Week 6 (Visit 4b, remitters only)

Notes:

[4] - 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: Per protocol, the end-point is reported using descriptive statistics only.

End point values	Remitters	Non-remitters		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4[5]	3[6]		
Units: hour				
median (full range (min-max))				
Visit 2	1.500 (1.00 to 2.00)	1.000 (0.500 to 2.00)		
Visit 4b	0.5000 (0.500 to 1.00)	0 (0 to 0)		

Notes:

[5] - PK analysis set.

[6] - PK analysis set. Visit 4b = 0 subjects

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Curve From 0 to Timepoint of the Last Detectable Plasma Concentration (AUC0-last)

End point title	Area Under the Curve From 0 to Timepoint of the Last Detectable Plasma Concentration (AUC0-last)[7]

End point description:

Venous blood samples (approximately 5 mL) for the determination of plasma concentrations of cobitolimod after administration of the study intervention, were collected through an indwelling venous catheter.

At Visit 4b, only the remitters were included.

End point type	Primary

End point timeframe:

Week 0 (Visit 2) and Week 6 (Visit 4b, remitters only)

Notes:

[7] - 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: Per protocol, the end-point is reported using descriptive statistics only.

End point values	Remitters	Non-remitters		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4[8]	3[9]		
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)				

Visit 2	110.6 (± 157)	47.59 (± 130)		
Visit 4b	27.04 (± 88.5)	0 (± 0)		

Notes:

[8] - PK analysis set.

[9] - PK analysis set. Visit 4b = 0 subjects

Statistical analyses

No statistical analyses for this end point

Primary: AUC From 0 to Infinity (AUCinf)

End point title	AUC From 0 to Infinity (AUCinf)[10]

End point description:

Venous blood samples (approximately 5 mL) for the determination of plasma concentrations of cobitolimod after administration of the study intervention, were collected through an indwelling venous catheter.

At Visit 2, the terminal elimination constant (lambdaz) could not be calculated for 6 out of 7 participants and subsequentially the lambdaz dependent PK parameter AUCinf could not be calculated. In the single participant (Non-remitter) where lambdaz could be calculated, the AUCinf was 26.4 h*nmol/L.

At Visit 4b, only the remitters were included.

End point type	Primary

End point timeframe:

Week 0 (Visit 2) and Week 6 (Visit 4b, remitters only)

Notes:

[10] - 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: Per protocol, the end-point is reported using descriptive statistics only.

End point values	Remitters	Non-remitters		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4[11]	3[12]		
Units: h*nmol/L				
geometric mean (geometric coefficient of variation)				
Visit 2	0 (± 0)	0 (± 0)		
Visit 4b	39.29 (± 117)	0 (± 0)		

Notes:

[11] - PK analysis set. Visit 4b = 3 subjects

[12] - PK analysis set. Visit 4b = 0 subjects

Statistical analyses

No statistical analyses for this end point

Primary: Half-life (T1/2)

End point title	Half-life (T1/2)[13]

End point description:

Venous blood samples (approximately 5 mL) for the determination of plasma concentrations of cobitolimod after administration of the study intervention, were collected through an indwelling venous catheter.

At Visit 2, the terminal elimination constant (lambdaz) could not be calculated for 6 out of 7 participants

and subsequentially the lambdaz dependent PK parameter T1/2 could not be calculated. In the single participant (Non-remitter) where lambdaz could be calculated, the plasma T1/2 was estimated to be 0.747 hours.

At Visit 4b, only the remitters were included.

End point type	Primary

End point timeframe:

Week 0 (Visit 2) and Week 6 (Visit 4b, remitters only)

Notes:

[13] - 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: Per protocol, the end-point is reported using descriptive statistics only.

End point values	Remitters	Non-remitters		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4[14]	3[15]		
Units: hour				
median (full range (min-max))				
Visit 2	0 (0 to 0)	0.747 (0.747 to 0.747)		
Visit 4b	1.852 (0.997 to 2.41)	0 (0 to 0)		

Notes:

[14] - PK analysis set. Visit 4b = 3 subjects

[15] - PK analysis set. Visit 4b = 0 subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency, Intensity and Seriousness of Adverse Events (AEs)

End point title	Frequency, Intensity and Seriousness of Adverse Events (AEs)

End point description:

AEs (including serious AEs [SAEs]) were collected from the start of study intervention administration until the end-of-study visit. The grading of the severity/intensity (grade 1 to grade 5) of AEs followed the common terminology criteria for AEs (CTCAE) v5.0. AEs were assessed as unlikely, possibly or probably related to the study intervention.

End point type	Secondary

End point timeframe:

From the start of study intervention administration until the end-of-study visit.

End point values	Remitters	Non-remitters		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4[16]	4[17]		
Units: Number of subjects				
Any AE	4	3		
Any SAE	0	0		
Any AE leading to withdrawal from study	0	1		
Any AE leading to death	0	0		
Causality to IMP - Possibly Related	0	3		
Causality to IMP - Unlikely Related	4	2		

Severity - Mild	3	3		
Severity - Moderate	2	1		
Severity - Severe	1	2		
Severity - Life-Threatening	0	0		
Severity - Death	0	0		

Notes:

[16] - Full analysis set.

[17] - Full analysis set.

Statistical analyses

No statistical analyses for this end point

Secondary: Clinically Significant Changes in Electrocardiogram (ECG)

End point title	Clinically Significant Changes in Electrocardiogram (ECG)

End point description:

Single 12-lead ECG was recorded in supine position after 10 minutes of rest using an ECG machine. Heart rate (HR) and PR, QRS, QT and QTcF intervals were recorded. Safety ECGs were reviewed and interpreted on-site by the Investigator.

Any abnormalities were specified and documented as clinically significant or not clinically significant. Abnormal post-dose findings assessed by the Investigator as clinically significant were reported as AEs.

There were no clinically significant trends in the overall ECG interpretations, no clinically significant change from baseline in ECG parameters and no clinically significant patterns in ECG associated with cobitolimod.

End point type	Secondary

End point timeframe:

At pre-defined time points from screening (Visit 1a) to End-of-study (Visit 5, Week 8)

End point values	Remitters	Non-remitters		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4[18]	4[19]		
Units: Number of subjects	0	0		

Notes:

[18] - Full analysis set.

[19] - Full analysis set.

Statistical analyses

No statistical analyses for this end point

Secondary: Clinically Significant Changes in Vital Sign

End point title	Clinically Significant Changes in Vital Sign

End point description:

Systolic and diastolic blood pressure and pulse were measured in supine position after 10 minutes of rest.

Any vital signs outside the normal ranges were judged as not clinically significant (NCS) or clinically significant (CS). The assessment was recorded in the eCRF. Post-study intervention vital signs judged as "abnormal, clinically significant" by the Investigator were reported as AEs.

There were no clinically significant changes from baseline in mean vital signs over time and no clinically significant vital signs patterns associated with cobitolimod

End point type	Secondary

End point timeframe:

At pre-defined time points from screening (Visit 1a) to End-of-study (Visit 5, Week 8)

End point values	Remitters	Non-remitters		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4[20]	4[21]		
Units: Number of subjects	0	0		

Notes:

[20] - Full analysis set.

[21] - Full analysis set.

Statistical analyses

No statistical analyses for this end point

Secondary: Clinically Significant Changes in Safety Laboratory Parameters

End point title	Clinically Significant Changes in Safety Laboratory Parameters

End point description:

Blood samples for analysis of clinical chemistry and haematology parameters were collected through venepuncture/an indwelling venous catheter and analysed by routine analytical methods. Faeces was analysed for gastrointestinal infections prior to enrolment. Calprotectin in faeces was analysed from stool samples that the participant brought to the clinic at Visits 2 and 4. Lab values outside the normal ranges were judged as not clinically significant or clinically significant.
There were no safety laboratory measurement values (including clinical chemistry and haematology) that were assessed as abnormal clinically significant. Individual abnormal laboratory values assessed as not clinically significant were noted. There were some trends in changes in mean laboratory parameters from baseline (Visit 1a) to end-of-study (Visit 4b, Day 42) and some minor differences in change between remitters and non-remitters for some parameters. The changes were assessed as not clinically significant.

End point type	Secondary

End point timeframe:

At pre-defined time points from screening (Visit 1a) to End-of-study (Visit 5, Week 8)

End point values	Remitters	Non-remitters		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4[22]	4[23]		
Units: Number of subjects	0	0		

Notes:

[22] - Full analysis set.

[23] - Full analysis set.

Statistical analyses

No statistical analyses for this end point

Secondary: Clinically Significant Changes in Physical Examinations

End point title	Clinically Significant Changes in Physical Examinations

End point description:

A complete physical examination included assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities. Any abnormalities were specified and documented as clinically significant or not clinically significant. Abnormal post-dose findings assessed by the Investigator as clinically significant were reported as AEs.

In general, no clinically significant abnormalities were observed during any physical examination. Occasional abnormal observations were assessed as not clinically significant.

End point type	Secondary

End point timeframe:

At pre-defined time points from screening (Visit 1a) to End-of-study (Visit 5, Week 8)

End point values	Remitters	Non-remitters		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4[24]	4[25]		
Units: Number of subjects	0	0		

Notes:

[24] - Full analysis set.

[25] - Full analysis set.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs (including serious AEs [SAEs]) were collected from the start of study intervention administration until the end-of-study visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Remitters

Reporting group description:

This group summarizes data for participants in remission (remitters).

Reporting group title	Non-remitters

Reporting group description:

This group summarizes data for participants not in remission (non-remitters)

Serious adverse events	Remitters	Non-remitters	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Remitters	Non-remitters	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	3 / 4 (75.00%)	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 4 (75.00%)	1 / 4 (25.00%)	
occurrences (all)	4	2	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	2	
Pyrexia			

subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	2	
Abdominal pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	2	
Colitis ulcerative			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	
occurrences (all)	2	1	
Lip swelling			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Infections and infestations			

COVID-19 subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 December 2021	Change to include participants with active ulcerative colitis instead of participants with active left-sided ulcerative colitis. Change to include participants who had previously been exposed to cobitolimod. Increased time window for conduct of Visit 4.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported