Clinical Trial Protocol

EXP-2177

Phase 2a trial to assess the efficacy and safety of LEO 152020 in adult patients with cholinergic urticaria

A randomised, double-blind, placebo-controlled, multi-site, cross-over trial

This clinical trial will be conducted in compliance with the clinical trial protocol, ICH GCP, and the applicable regulatory requirement(s).

LEO Pharma A/S	**Trial ID:**	**EXP-2177**
	Date:	**08-Apr-2022**
	EudraCT no:	**2020-004961-38**
	Version:	**7.0**

Clinical trial protocol statements

Approval statement LEO Pharma A/S

Electronic signatures made within eTMF LEO are considered to be a legally binding equivalent of traditional handwritten signatures. The following persons have approved this clinical trial protocol by using electronic signatures as presented on the last page of this document:

PPD, MMath, PhD
Biostatistics lead, Medical Sciences

PPD, MD, DMSc.
Medical lead, Translational Medicine, Research & Early Development

PPD, MD
Senior Director, Medical Department

PPD, MSc. Pharm.
Clinical operations lead, Global Clinical Operations

PPD, MD
Signatory investigator

Acknowledgement statement investigator(s)

Each participating investigator must agree to the approved clinical trial protocol by signing a clinical trial protocol acknowledgement form or similar document.

Protocol amendment summary of changes table

Document history

Document	**Date**	**Type of protocol amendment**
Amendment 6 (substantial)	08-Apr-2022	global
Amendment 5 (substantial)	09-Mar-2022	global
Amendment 4 (non-substantial)	06-Dec-2021	global
Amendment 3 (substantial)	15-Jun-2021	global
Amendment 2 (non-substantial)	16-Apr-2021	global
Amendment 1 (substantial)	09-Mar-2021	global
Original protocol	12-Jan-2021	NA

Protocol amendment summary of changes tables for previous amendments (Amendment 1, dated 09-Mar-2021, Amendment 2, dated 16-Apr-2021, Amendment 3, 15-Jun-2021, Amendment 4, dated 06-Dec-2021, and Amendment 5, dated 09-Mar-2022) are provided in Appendix 7.

Amendment 6 (08-Apr-2022)

This amendment is considered substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union or subsequent regulation.

Overall rationale for the amendment:

With the introduction of COVID-19 vaccines, COVID-19 may now be considered more like other influenza-like diseases – and COVID-19 (confirmed by a positive SARS-CoV-2 test result) is no longer deemed a major health risk as disease symptoms are commonly only mild and patients rapidly recover from COVID-19. This amendment is intended to take account for the changed status of the COVID-19 pandemic.

Section no. and name	**Description of change**	**Brief rationale**
8.3 Exclusion Criteria & Appendix 5 Short version of eligibility criteria	Exclusion criterion 13 has been modified: Formerly: 13. Subjects with confirmed active infection with SARS-CoV-2 and related disease (COVID-19). New: 13. Subjects with confirmed active infection with SARS-CoV-2 **AND** related COVID-19 **symptoms, which at the discretion of the investigator will jeopardize the safety of the subject or the integrity of the data collected. Additionally, any local requirements must be followed.**	The amendment reflects the changed status of COVID-19. It is important to note the investigational drug is not presumed to interfere with the immune response against COVID-19. With this amendment we will allow patients with a positive COVID-19 test and with no or mild symptoms to be enrolled or to remain in this clinical trial. The decision to be enrolled or to remain in the trial despite a positive COVID-19 test will be at investigator's discretion to safeguard patient safety and as long as in line with local regulations.

Section no. and name	**Description of change**	**Brief rationale**
10.2.1 Reasons for permanent discontinuation of IMP	Rewording of the reason for permanent discontinuation of IMP due to SARS-CoV-2 infection Formerly: Subjects will permanently discontinue IMP in any of the treatment periods in the event of: • …. • Infection with COVID -19 • …. New: Subjects will permanently discontinue IMP in any of the treatment periods in the event of: • …. • Symptomatic infection with SARS-CoV-2 that is likely to have an impact on efficacy or safety data (i.e., patients with a SARS-CoV-2 infection without or very mild symptoms only (e.g., rhinitis or sore throat) might continue with the study at investigator's discretion and in accordance with the applicable local regulations). • ….	The adjustment was again made in the light of the changing course of disease in case of infection with SARS-CoV-2, which currently tends to show milder courses and shorter durations due to the vaccination status but also the dominant viral variant. The infection situation will continue to be monitored and necessary adjustments will be implemented as needed.

Section no. and name	**Description of change**	**Brief rationale**
11.4.5 Test for SARS-CoV-2 infection	Rewording of the section on procedure for patients with confirmed SARS-CoV-2 infection. Formerly: Subjects with active and confirmed SARS-CoV-2 infection will be managed in accordance with institutional guidelines with regards to trial site visits. In case of confirmed SARS-CoV-2 infection the subject will be withdrawn from trial. New: Subjects with active and confirmed SARS-CoV-2 infection will be managed in accordance with institutional guidelines with regards to trial site visits. ~~**In case of confirmed SARS-CoV-2 infection the subject will be withdrawn from trial.**~~	To align with section 10.2.1 "Reasons for permanent discontinuation of IMP".

Section no. and name	**Description of change**	**Brief rationale**
Clinical trial protocol statements	PPD has been replaced by PPD as Senior Director, Medical Department at LEO Pharma A/S	Due to personnel changes and changes in project responsibility at LEO Pharma A/S, it is necessary to adapt the Approval Statement accordingly

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List of abbreviations

AD	Atopic dermatitis
AE	adverse event
AESI	adverse event of special interest
AUC	Area under the curve
BCRP	Breast cancer resistance protein
CCI	[redacted]
BP	blood pressure
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CMO	contract manufacturing organisation
CholU	Cholinergic urticaria
CholUAS7	Cholinergic Urticaria Activity Score 7
CholUQoL	Cholinergic Urticaria Quality of Life questionnaire
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRA	clinical research associate
CRO	contract research organisation
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CTR	clinical trial report
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
ET	early termination visit
FAS	Full Analysis Set
FcεRI	high-affinity receptor for the Fc region of immunoglobulin E
FU	follow-up visit
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
anti-HBc	Hepatitis B core antibody

H4R	histamine H4 receptor
hCG	human chorionic gonadotropin
HCP	healthcare professional
HDL	High density lipoprotein
HIV	human immunodeficiency virus
HSS(7)	hive severity score; HSS7: weekly score
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification number
IEC	independent ethics committee
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E
IL	Interleukin
IMP	investigational medicinal product
ISF	Investigator Site File
ISS(7)	Itch severity score; ISS7: weekly score
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LDL	Low density lipoprotein
MAD	Multiple-ascending dose
MCID	minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
NBUVB	narrow band ultraviolet B]
NOAEL	No Observed Adverse Effect Level
OAT3	Organic anion transporter 3
PD	pharmacodynamics
PhGA	Physician's Global Assessment
PGI-S	Patient's Global Assessment of Severity
P-gp	permeability glycoprotein
PK	pharmacokinetics
PO	Per os (oral administration)
PPS	Per Protocol Analysis Set

PRO	patient-reported outcome
PT	preferred term
PUVA	Psoralen + ultraviolet A
QoL	Quality of Life
QTc(F)	Q-T corrected interval (by Fredericia)
SAD	Single-ascending dose
SAE	serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SDTM	Study Data Tabulation Model
SOC	system organ class
SPT	Skin Prick Testing
SUSAR	suspected, unexpected serious adverse reactions
TEAE	Treatment emergent adverse event
Th1/Th2	T helper cells type 1/type 2
TSLP	Thymic stromal lymphopoietin
UASprovo	Urticaria Activity Score post-provocation
(m)UCT	(modified) Urticaria Control Test
UVA / UVB	ultraviolet A and ultraviolet B
VAS	Visual Analogue Scale
WHO	World Health Organization
WOCB	Woman of childbearing potential

1 Protocol synopsis

<table>
<tr><td>Trial ID
EudraCT no.</td><td>EXP-2177
2020-004961-38</td></tr>
<tr><td>Title of trial</td><td>Phase 2a trial to assess the efficacy and safety of LEO 152020 in adult patients with cholinergic urticaria</td></tr>
<tr><td>Short title of trial</td><td>Phase 2a trial to assess the efficacy and safety of LEO 152020 in adult patients with cholinergic urticaria</td></tr>
<tr><td>Main objective(s) and endpoint(s)</td><td>
<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td>Primary objective</td><td></td></tr>
<tr><td>To explore the efficacy of LEO 152020 compared with placebo in patients with CholU.</td><td>Time frame: baseline of each treatment period to end of each treatment period
Primary efficacy endpoint
• Change from baseline in post-provocation Urticaria Activity Score (UASprovo).
Other/exploratory efficacy endpoint(s)
[redacted]</td></tr>
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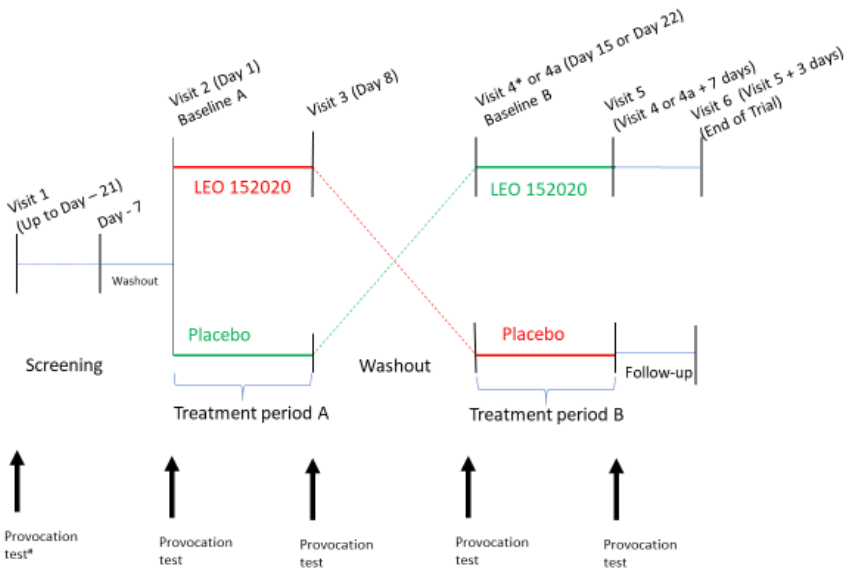
		[redacted]
	Secondary objective(s)	
	To evaluate the safety of LEO 152020 compared with placebo in patients with CholU.	*Secondary endpoint* • Number of treatment emergent adverse events (TEAE) per subject. Time frame: start treatment period to 3 days after end treatment period
	Other/exploratory objectives	
	To explore the expression of biomarkers of LEO 152020 compared with placebo in patients with CholU.	*Other/exploratory endpoint(s)* [redacted]
	To explore the pharmacokinetics of LEO 152020 in patients with CholU.	*Other/exploratory endpoint(s)* [redacted]
Final collection of data for the primary endpoint	Visit 5 (7 days after baseline of treatment period B)	
Trial design	EXP-2177 is a phase 2a, randomised, double-blind, placebo-controlled, multi-centre, cross-over trial conducted in Germany. Subjects will be randomised, stratified by site to one of two treatment sequences. Each treatment period will last 7 days with a wash-out period of 7 days between treatments. Safety follow-up visit will be performed 3 days after last IMP dose.	

	
Main assessments	**<u>Efficacy assessments:</u>** **Urticaria Activity Score post-provocation (UASprovo):** After Pulse-controlled ergometry (PCE) provocation test subjects will be rated on their number of wheals and their itch severity, resulting in a sum score for the UASprovo ranging from 0 to 6 points: a) Numbers of wheals (0 wheals = 0; 1 to 20 wheals = 1; 20 to 50 wheals = 2; > 50 wheal = 3) b) Itching (none = 0, mild = 1, moderate = 2, severe = 3). **Histamine Skin Prick Testing (SPT):** Test for histamine sensitivity causing pruritus, skin flare and a skin wheal. The absolute wheal/flare size will be measured. A positive test is defined as a wheal and flare reaction (≥ 3mm in diameter relative to negative control). Pruritus during the SPT will be assessed by subjects every minute for 15 minutes in total using a 100mm VAS scale with 0 indicating 'no itch' and 10 indicating 'worst itch imaginable'. **Physician's Global Assessment (PhGA):** Instrument to rate the severity of the subject's current disease severity using a Visual Analogue Scale (VAS) ranging from 0 (absence) to 10 (worst possible severity). **Patient Reported Outcomes (PROs):** **Patient's Global Assessment of Severity (PGA-S):** Single item designed to capture the subject's overall perception of their symptoms over the past week on a Visual Analogue Scale ranging from 0 (absence) to 10 (worst possible severity). **Urticaria Control Test (UCT):** Disease-specific measure consisting of four questions that retrospectively assesses patients' burden of disease over the previous 4 weeks and, in addition, over the past week (mUCT) to capture changes over a shorter recall period. Concepts covered include disease activity, QoL survey, disease control, and therapy. Each of the four questions are scored on a scale of 0 to 4. The UCT score is derived by adding up the scores from each of the four questions. A total score from 0

	(no control) to 16 points (complete control) is derived, with a score of ≥ 12 indicating well-controlled disease. **Cholinergic Urticaria Activity Score 7 (CholUAS7):** Validated tool to assess disease symptoms in CholU subjects. The weekly CholUAS7 is the sum of the daily Hive Severity Score (HSS) and the daily Itch Severity Score (ISS) for 7 consecutive days, each ranging between 0 and 3 per day. The possible range of the weekly CholUAS7 score is 0-42 with higher values indicating higher disease severity. **Safety assessments:** • Adverse Events, • Vital signs (resting blood pressure, pulse, and body temperature), • Physical examination • ECG (12-lead resting digital ECG; pre-dose at screening and 1 h post-dose at visit 2 to visit 5) • Central / Local laboratory testing (haematology, blood chemistry, serology, pregnancy test and SARS-CoV-2).
Main criteria for inclusion	• Subject with a history of CholU diagnosis for ≥ 6 months, • Subject has active and uncontrolled CholU disease at the time of screening and randomisation, as defined by the following: a. Urticaria control test (UCT) < 12 at screening b. UASprovo ≥ 3, • Age 18 or older, • Recent history (within 6 months of screening) with documented inadequate response to standard dose as to marketing authorization of H1 antihistamines.
Main criteria for exclusion	• Other clearly dominating forms* of urticaria as aetiology for wheal and flare type reactions, *These diseases are allowed as comorbidities, if cholinergic urticaria is the dominating form of chronic urticaria, • Systemic immunosuppressive medications within 4 weeks prior to screening, • Systemic drugs (e.g. oral drug) with antihistamine properties including H1 antihistamines and H2 antihistamines 1 week prior to randomisation. However, topical antihistamines in the form of nasal spray and eyedrops are allowed in the standard prescribed dose.
Investigational medicinal product(s)	Name of IMPs: **LEO 152020 film-coated tablet** • Active substance: LEO 152020 • Dosage form: film-coated tablet • Concentration: CCI [redacted] • Dose: CCI [redacted] • Method of administration: oral **Placebo film-coated tablet** • Active substance: not applicable

	• Dosage form: film-coated tablet • Concentration: not applicable • Dose: CCI • Method of administration: oral
Duration of trial participation	Up to 8 weeks in total: • up to 3 weeks screening period • 1 week: treatment period A • 1 week: wash-out period – may be prolonged by 1 week if start of treatment period B needs to be postponed due to retest of UASprovo • 1 week: treatment period B • Up to 1 week follow-up period
Number of subjects	A total of 28 subjects will be randomised 1:1 to the treatment sequences in this cross-over trial
Number and distribution of trial sites	Approximately 3-6 sites in Germany
Statistical methods	The primary efficacy endpoint will be compared between treatments by means of a linear mixed model, containing treatment, period and carryover effects, the factor site, and UASprovo at treatment start within period as covariate. Null hypothesis is that the endpoints are equal for both treatments against the alternative that they are different. The primary analysis will be performed for the full analysis set.
Signatory investigator	PPD , MD PPD Berlin, Germany
Sponsor	LEO Pharma A/S, Industriparken 55, 2750 Ballerup, Denmark

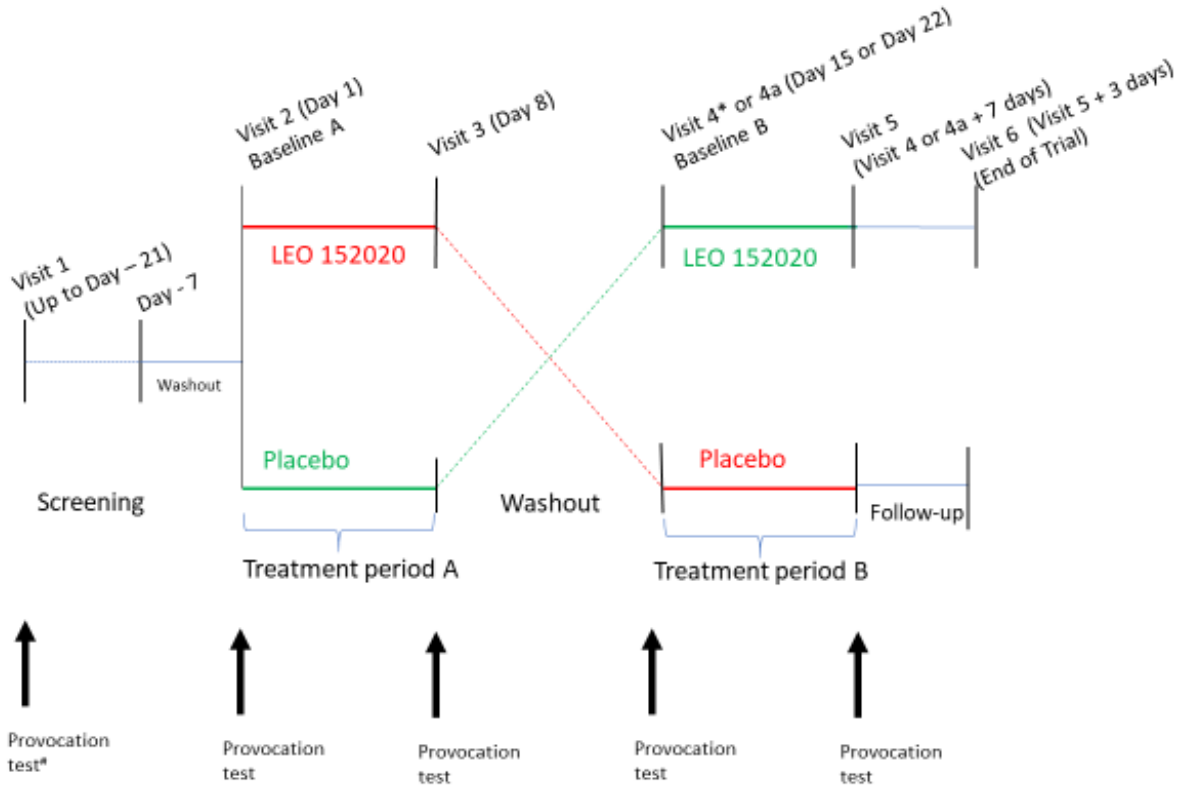
2 Trial identification

EudraCT number: 2020-004961-38

The clinical trial protocol will be registered in local registries if required by local legislation.

3 Schematic of trial design

Panel 1: Trial design



*Similar to visit 2, at visit 4 the subject will be required to demonstrate a UASprovo ≥ 3 (with a minimum wheal score of ≥ 1 and minimum itch score of ≥ 1) in order to progress to treatment period B. If the subject does not demonstrate a UASprovo ≥ 3 they will be required to attend an additional study visit (visit 4a) 7±1 days later (see additional details in Panel 2).

#Screening provocation test is optional if patients had a recent provocation test within 6 months of day 1 (visit 2)

IMP(s):

- Sequence 1) LEO 152020 CCI during treatment period A and placebo tablets CCI during treatment period B,
- Sequence 2) placebo CCI during treatment period A and LEO 152020 CCI during treatment period B.

4 Schedule of trial procedures

Panel 2: Schedule of trial procedures

For sequence of assessments during the visits please refer to Section 11.1

	Screening	Treatment period A		Wash out	Treatment period B			Follow-up	ET[1]	References (protocol section)
Visit	**1**	**2 (Baseline A)**	**3**		**4* (Baseline B)**	**4a** (Baseline B)**	**5**	**6**		
Day	**-21 (-7)*** to -1**	**1**	**8**		**15**	**V4 + 7**	**Baseline B + 7**	**V5 + 3**		
Visit window (days)	**N/A**	**N/A**	**-1 to + 3**		**±1**	**±1**	**-1 to + 3**	**+4**		
Informed consent(s)	X									Appendix 3B
Subject eligibility	X	X								8.2 and 8.3
Demographics	X									11.2.1
Medical history	X									11.2.2
Height and weight	X									11.2.3
Concomitant medications/and procedures	X	X	X		X	X	X	X	X	9.6
Diary handout	X									
Diary review/collection of completed pages		X	X		X	X	X	X	X	
Diary completion	←==========							==========→		11.7.1.1

	Screening	Treatment period A		Wash out	Treatment period B			Follow-up	ET[1]	References (protocol section)
Visit	**1**	**2 (Baseline A)**	**3**		**4* (Baseline B)**	**4a** (Baseline B)**	**5**	**6**		
Day	**-21 (-7)*** to -1**	**1**	**8**		**15**	**V4 + 7**	**Baseline B + 7**	**V5 + 3**		
Visit window (days)	**N/A**	**N/A**	**-1 to + 3**		**±1**	**±1**	**-1 to + 3**	**+4**		
Trial products and randomisation										
Randomisation		X								9.3
IMP dispensation		X			X	X				9.8
IMP use[a]		X	X		X	X	X			9.2
IMP return			X				X			9.8
Compliance control			X				X			9.8.4
Investigator assessments of efficacy										
UASprovo (incl. Time until sweating/whealing)	X[b]	X	X		X*	X	X		X	11.3.1
Physician's global assessment by VAS		X	X		X	X	X			11.3.2
Histamine SPT (wheal size + pruritus VAS)		X	X		X*	X	X			11.3.3
Patient assessments										
CholUAS7		X	X		X	X	X			11.3.4.3
UCT	X	X[c]	X[c]		X[c]	X[c]	X[c]			11.3.4.2

	Screening	Treatment period A		Wash out	Treatment period B			Follow-up	ET[1]	References (protocol section)
Visit	**1**	**2 (Baseline A)**	**3**		**4* (Baseline B)**	**4a** (Baseline B)**	**5**	**6**		
Day	**-21 (-7)*** to -1**	**1**	**8**		**15**	**V4 + 7**	**Baseline B + 7**	**V5 + 3**		
Visit window (days)	**N/A**	**N/A**	**-1 to + 3**		**±1**	**±1**	**-1 to + 3**	**+4**		
DLQI		X	X		X	X	X			11.7.1.2
CholU-QoL[d]		X	X		X	X	X			11.7.1.3
Patient's global assessment by VAS		X	X		X	X	X			11.3.4.1
Safety and lab measurements										
Physical examination	X	X	X		X*	X	X	X		11.4.2
Vital signs	X	X	X		X*	X	X	X		11.4.1
ECG	X[e]	X[f]	X[f]		X[f]	X[f]	X[f]	X[g]		11.4.3
SARS-CoV-2 screening[h]	X	X	X		X	X	X	X		11.4.5
Serum pregnancy test (WOCB only)	X									11.4.4.1
Urine pregnancy test (WOCB only)		X			X*	X		X		11.4.4.1
Hepatitis B, C, and HIV	X									11.4.4.1
Serum chemistry and haematology	X		X				X	X	X	11.4.4.1
Adverse events	X	X	X		X	X	X	X	X	13.2
Skin biopsy[i]		X	X							11.6.2

	Screening	Treatment period A		Wash out	Treatment period B			Follow-up	ET[1]	References (protocol section)
Visit	**1**	**2 (Baseline A)**	**3**		**4* (Baseline B)**	**4a** (Baseline B)**	**5**	**6**		
Day	**-21 (-7)*** to -1**	**1**	**8**		**15**	**V4 + 7**	**Baseline B + 7**	**V5 + 3**		
Visit window (days)	**N/A**	**N/A**	**-1 to + 3**		**±1**	**±1**	**-1 to + 3**	**+4**		
Blood sampling biomarkers[j]		X	X		X	X	X			11.6.1
PK blood sampling[k]		X	X		X	X	X			11.5.1
Photography of biopsy site[l]		X	X							11.7.2
End of trial								X	X	11.8

1. In addition to the regular safety FU-visit (Visit 6) a shortened early termination visit (ET) should be performed as soon as possible after the last administration of the IMP, but not more than 3 days after the last use of the IMP for subjects prematurely withdrawn from trial for any reason. If no early termination visit can be performed within this time frame (i.e. within 3 days after the last use of the IMP), the safety follow-up visit should be performed as the last visit, only.

* At visit 4, the subject will be required to demonstrate a UASprovo ≥ 3 (with a minimum wheal score of ≥ 1 and minimum itch score of ≥ 1) in order to progress to treatment period B. If the subject does not demonstrate a UASprovo ≥ 3, only assessment marked with * will be performed and an additional study visit will be scheduled (visit 4a) 7±1 days later.

**Visit 4a is only performed if subject failed to demonstrate a UASprovo ≥ 3 at V4. If at visit 4a the subject demonstrates a UASprovo ≥ 3 then they will progress to treatment period B. If at visit 4a the subject does not demonstrate a UASprovo ≥ 3, then they will be terminated from the trial and an early termination visit will occur.

*** The screening visit (visit 1) has to be conducted at least 7 days prior to the baseline visit (visit 2) to ensure a 7-day documentation of the ChloUAS (in the patient's diary) for calculation of the CholUAS7 at baseline visit (visit 2), and if applicable to respect a) a minimum interval of 7 days between two UAS provocation tests and/or ,b) a 1-week washout period for systemic antihistamines and/or medications with antihistamine properties. However, the use of topical antihistamines (e.g. with nasal sprays or eyedrops) for the treatment of concomitant allergies is allowed to be continued if applied in the standard prescribed dose.

a. First daily dose of IMP at visits under treatment (V2 to V5) will be administered on site, preferably in the CCI

b. Screening provocation test is optional if patients had a prior provocation test within 6 months of day 1 (visit 2). If subject fails to meet inclusion threshold during screening provocation test, then they are allowed one additional screening attempt. There should be at least 7 days between provocation tests, including between screening provocation test and visit 2 provocation test.

c. UCT: Standard UCT has a recall period of 4 weeks. For screening, the standard UCT will be used. For visits 2-5, a modified UCT with a recall period of 7 days will be utilized.

d. Chol-QoL: Standard Chol-QoL has a recall period of 2 weeks. For visits 2-5, a modified Chol-QoL with a recall period of 7 days will be utilized.

e. At screening 3 consecutive ECGs will be measured and the average QTcF derived.

f. One post-dose ECG will be performed 1h (±15 min) after the administration of the IMP on site to determine the theoretic maximum of QT-prolongation. For subjects who experienced a moderate or severe QT prolongation, the ECG should be repeated at respective visit(s) to confirm QT-prolongation. A subject may continue with the trial as long QT-prolongation does not exceed QTcF > 500 ms or a change in QTcF from baseline (pre-dose ECG) > 60 ms,

g. For subjects who experienced a moderate QT prolongation (defined as 480 ms < QTcF ≤ 500 ms or 30 ms < change in QTcF from baseline (pre-dose ECG) ≤ 60 ms during the trial) an additional ECG should be made at safety follow-up (visit 6).

h. SARS-CoV-2 test is required for all subjects at screening. At subsequent visits subjects will be monitored for SARS-CoV-2 infection signs and symptoms. If SARS-CoV-2 infection is suspected, a SARS-CoV-2 test should be performed. Subjects with confirmed SARS-CoV-2 infection will be managed in accordance with institutional guidelines and local requirements.

i. Skin biopsies will be optional. Subject will sign an additional informed consent form. At visit 2, subjects will have a total of four 3 mm punch biopsies performed at 2 timepoints: 2 non-lesional skin biopsies (from an area, that usually develops wheal and flare upon provocation), taken prior to the provocation test and 2 lesional skin biopsies taken after the provocation test. At visit 3, subjects will have two biopsies performed on non-lesional skin (from an area, that usually develops wheal and flare upon provocation) prior to the provocation test.

j. Serum sampling for biomarker analysis at baseline visits (i.e. V2 and V4/4a) should be taken prior to the intake of the IMP and sampling at the end of treatment visits (i.e. V3 and V5) for each of the treatment periods should be done after the IMP intake.

k. At visit 2 and visit 4/4a, PK blood samples should be taken approximately CCI after IMP intake at site. At V3 and V5, PK blood samples should be taken prior to administration of the IMP on site, and approximately CCI after administration of the IMP on site.

l. Photography of the skin biopsy site will only be performed in patients who opt in for skin biopsies.

Abbreviations: ET – early termination visit; UASprovo – post-provocation Urticaria Activity Score, CholUAS7 - Cholinergic Urticaria Activity Score, UCT - urticaria control test, DLQI - dermatological quality of life index, CholU-QoL - cholinergic urticaria quality of life questionnaire, histamine SPT – histamine skin prick testing, VAS - visual analogue scale, WOCP – Woman of childbearing potential, HIV – human immunodeficiency virus, SARS-CoV-2 - Severe acute respiratory syndrome coronavirus 2, ECG – electrocardiogram, QTcF – Q-T corrected interval (by Fredericia), PK – pharmacokinetic IMP – investigational medicinal product.

5 Introduction and trial rationale

5.1 Cholinergic urticaria

Cholinergic urticaria (CholU) is a very frequent form of chronic inducible urticaria [1, 2]. CholU is defined by itching and whealing following the induction of sweating, either actively (e.g. exercise) or passively (e.g. hot bath, sauna). CholU is typically a disorder of young adults (~20 - 30 years old) with a high prevalence in the age group of 26 to 28 years (up to 20%) [2]. CholU patients typically develop pruritic, pinpoint-sized, transient wheals with large flare reactions commonly localized to the limbs and the trunk a few minutes after the onset of sweating. The wheals in CholU patients are extremely itchy. In some patients, emotional stress, hot and spicy food, and hot beverages can also elicit symptoms. Usually, skin lesions last for 15 to 60 minutes. CholU is often associated with atopy [2, 3] and bronchial hyper-responsiveness [4].

CholU is a histamine-driven chronic inflammatory disease involving mast cells, basophils, and eosinophils. Several recent studies suggest that CholU may be an allergy to components of human sweat. First, CholU patients show immediate-type hypersensitivity reactions to their own diluted sweat after intradermal injections [5]. Second, basophils from CholU patients react to autologous sweat and release high amounts of histamine *in vitro* [6]. Finally, CholU patients, but not healthy controls, express immunoglobulin E (IgE) to sweat antigens [7].

5.2 Experience with investigational medicinal product

LEO 152020 is a selective, oral histamine H4 receptor (H4R) antagonist with expected dual anti-pruritic and anti-inflammatory effects, and is being developed to be offered as an oral treatment option for atopic dermatitis (AD) [8].

LEO 152020 has been tested preclinically in various in vitro models and have shown CCI [redacted] In functional assays, LEO 152020 has been characterized as a CCI [redacted] of the H4R.

As LEO 152020 is still at an early stage of development only non-clinical and limited clinical data are available.

Non-clinical studies have demonstrated that LEO 152020 appears to be safe considering a CCI [redacted] and adequate safety margins have been established. The important potential risks and the safety concerns included in the following sections are based

on the knowledge of the available nonclinical data and clinical single-ascending dose (SAD)/multiple-ascending dose (MAD) data, as well as events observed with other H4R antagonists [8].

One first-in-human clinical trial containing SAD and MAD parts with overall 88 subjects was completed. Emerging tolerability issues were observed in the CCI cohort (highest dose tested), CCI and CCI CCI cohort. These consisted of mild (grade 1) and transient gastrointestinal adverse events (primarily nausea, abdominal distention, and diarrhea) and nervous system disorders (dizziness - grade 1). All events mentioned above occurred rapidly after dosing and the majority of events resolved within 1 to 3 hours. These adverse events were not considered a safety concern. Of note, no tolerability issues were observed in CCI cohort, in CCI cohort, in CCI cohort, or in any lower dose cohorts. The potential risk of QT prolongation (delay of cardiac repolarization) was identified based on nonclinical and clinical data. In the data from the SAD segment, the predicted mean and 90% CI ΔΔQTcF (Q-T corrected interval by Fredericia) obtained from concentration-QTcF analysis, at each dose Cmax geometric means, showed that the prolongation in QTcF was above the threshold of regulatory concern of 10 msec (Guideline ICH E14) from the doses of CCI. At CCI the mean ΔΔQTcF was around CCI Therefore, it can be concluded that up to the dose of CCI mg, the upper bound of the 90% CI for ΔΔQTcF was below the threshold of regulatory concern of 10 msec. However, for the doses CCI and CCI mg, both the mean ΔΔQTcF and the 90% CI upper bound were CCI.

Safety precautions such as additional ECG monitoring and exclusion of subjects with known cardiac arrhythmia risk factors, exclusion of subjects with renal and hepatic impairment, exclusion of concomitant medication with known QT-prolongation effects as well as prohibition of concomitant medications that are inhibitors of the permeability glycoprotein (P-gp) and Breast cancer resistance protein (BCRP) transporters and the strong OAT3 (organic anion transporter 3) inhibitor probenecid, which may increase systemic exposure of LEO 152020 will be implemented for the clinical trials and therefore the dose of CCI is considered acceptable to be administered (for further information please refer to the investigator's brochure (IB) [8]).

5.3 Trial rationale

Histamine exerts its inflammatory effects by acting on its receptors. Both H1 receptors (H1R) and H4 receptors (H4R) have important roles in the progression and modulation of histamine-mediated allergic and inflammatory diseases. The first line treatment options in CholU are avoidance of eliciting triggers and the daily use of non-sedating H1 antihistamines. However, many CholU patients do not achieve disease control with these measures [9]. Updosing of H1-antihistamines, the guideline-recommended treatment of choice in these patients, is only moderately effective.

Antagonists that target H4R have shown promising effects in preclinical and clinical studies in the treatment of several allergic and inflammatory diseases [10].

H4R activation mobilizes intracellular calcium to prime mast cells for activation and degranulation [11]. H4R activation also upregulates the expression of high-affinity receptor for the Fc region of immunoglobulin E (FcεRI) on mast cells, further priming them for allergen-induced activation. In CholU, skin mast cells are activated to degranulate, at least in part, via FcεRI and IgE to autoallergens [5, 6].

Eosinophils express H4R on their surface and histamine, acting via H4R, enhances the migration of eosinophils. Eosinophil shape change is a necessary process for chemotaxis to occur. Histamine and selective H4R agonists were shown to induce the shape change of eosinophils, an effect that is blocked by selective H4R antagonists [12, 13]. Skin biopsies of CholU lesions show histologic characteristics identical with those of other forms of urticaria including the presence of eosinophils in and around the walls of superficial subpapillary dermal vessels [14].

H4R may be involved in the pathogenesis of allergy and inflammation by activating Th2 (T helper cells) pathways. H4R is preferentially expressed in Th2 cells over naive T cells and Th1 cells [15]. Recent findings have shown that activation of H4R by histamine stimulates the synthesis of the Th2 cytokines IL-4 and IL-5 in mast cells [11]. Chronic urticaria is characterized by the emergence of Th2-type cytokines, including IL (interleukin)-4, IL-5, IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), which favour antibody isotype class switching to IgE, along with the presence of eosinophils and mast cells [16]. Patients with CholU exhibit increased levels of IgE [17] as well as increased numbers of skin mast cells and eosinophils [14].

Results from a pilot study on the characterization of lesional and non-lesional skin of CholU for the expression levels of all four histamine receptors suggest that H4R is markedly

upregulated in the skin of CholU patients as compared to healthy controls (data from PPD). Several independent lines of evidence support the notion that the use of an H4R antagonist is an effective treatment option for patients with CholU.

5.4 Ethical considerations

This clinical trial will be conducted in accordance with the ethical principles originating from the Declaration of Helsinki [18] and ICH GCP [19] and in compliance with the approved protocol and applicable regulatory requirements.

The trial design is considered scientifically justified and adheres to ethical standards ensuring the rights, safety, and well-being of the subject. The efficacy and safety of LEO 152020 will be evaluated in adults with CholU who may benefit from treatment with LEO 152020.

For this very early phase evaluation of clinical efficacy an intra-individual comparison has been chosen requiring much fewer participants to potentially detect a statistically significant difference between treatments than a trial with inter-individual comparison of treatments. Only adult subjects aged at least 18 years will be included in the trial. Pregnant or breastfeeding women and women trying to become pregnant will not be enrolled in this clinical trial. Men and women of child-bearing potential have to agree to use a double method of contraception to prevent pregnancy during the clinical trial and until at least 3 days after discontinuation of treatment with the IMP. In addition, all females will have a pregnancy test performed before, during and at the End of Trial to ensure that no fetuses are exposed to the IMP. In accordance with the current version of ICH and GCP guidelines, qualified medical personnel will readily be available to advise on trial related medical questions. Medical monitoring will be conducted throughout the trial. Safety data will be reviewed by qualified personnel to ensure that prompt action is taken, if needed to protect the subject.

5.5 Benefit/risk assessment

The first line treatment for chronic urticarias, such as CholU, is standard dose as to marketing authorization second generation H1 antihistamines, however the majority of patients fail to achieve disease control. Even with increased doses up to four times standard dose H1 antihistamines (second line treatment), a large portion of chronic urticaria patients will not control symptoms, and therefore there is a clear unmet need for a safe, efficacious treatment option for subjects with CholU. As a novel oral H4R antagonist, LEO 152020 is expected to be efficacious against both wheal formation and pruritus caused by CholU.

Other treatment options especially for patients unresponsive to 2nd generation H1 antihistamines include omalizumab (recommended as third line treatment) and immunosuppressives (e.g. Ciclosporin A, recommended as fourth-line treatment only, due to the higher incidence of adverse effects of Ciclosporin A, when compared to 2nd generation H1 antihistamines). As both of these treatment options are not considered as a standard of care for different reasons, and due to the short duration of the treatment with LEO 152020, the use of LEO 152020 is considered justified in light of a possible future treatment option for subjects with CholU. This is especially true given that H4R antagonists have already shown promising effects in the treatment of various allergic and inflammatory diseases in preclinical and clinical studies. Therefore, it seems to be also reasonable to assume that patients will have a potential benefit from their participation in the study, even if they have no other treatment option for the duration of the trial.

Risks to subjects in the trial will be minimized by inclusion of subjects fulfilling all eligibility criteria (Sections 8.2 and 8.3) and by close clinical monitoring. Discontinuation and withdrawal criteria are also in place (Section 10.2). All subjects will receive both active and placebo during this cross-over trial. Active treatment with LEO 152020 at the proposed dose regimen is expected to have a therapeutic effect (based on biomarker analysis in the first in human trial with LEO 152020 [8] and modelling of data from a clinical trial with Adriforant [20]).

Blood sampling presents the same low risk as normally associated with this procedure (i.e. infection, bleeding into the surrounding tissue, and, very rarely, inflammation of the vein or formation of blood clots). Blood sampling will only be conducted by qualified medical personnel.

Subjects who consented to skin biopsies may experience discomfort associated with the collection of the samples. To minimize discomfort, the subject will receive an injection of a local anesthetic to numb the area where the biopsy will be taken. Subjects who have previously had reactions to an aesthetic medication will not be included in this component of the trial. Complications of skin biopsies may include bleeding, infection, bruising and/or pain at the biopsy site. Pressure dressings and ice may be used to help alleviate these symptoms. Wound healing at the biopsy site will be checked at a subsequent visit and sutures removed as needed. The subject will be informed that they may retain small scars after the procedure.

Due to the important potential risk of QT prolongation, the choice of dose regimen explored in this trial was guided by modelling exposure vs. QTcF observed in the first in human trial with LEO 152020. Based on this modelling, the mean increase in QTcF as a result of

treatment with LEO 152020 CCI is expected to be below regulatory and safety concern. To further ensure subject safety, subjects at cardiac arrhythmia risk and subjects with renal and hepatic impairment will be excluded from participation in the trial (Section 8.3). Moreover, medications for which QT prolongation is a known side effect and medications known to inhibit the BCRP and/or P-gp transporters and the strong OAT3 inhibitor probenecid will be prohibited during the trial. Subjects undergoing treatment with these and not able to replace them by safe alternative medication(s) will be excluded from participation in the trial. Finally, frequent ECG monitoring will be conducted with pre- and/or post-dose ECGs measured at the sites and evaluated centrally (Section 11.4.3). ECG measurements will be combined with measurements of LEO 152020 plasma concentration at Cmax to further evaluate the relation between exposure to LEO 152020 and potential QT prolongation at therapeutic doses in subjects with CholU. With the above provisions in place, the risks associated with participating in the trial are considered low and outweighed by the benefit of a potential future oral treatment option for CholU. The current risk profile is therefore deemed in favor of continued development of LEO 152020, however the investigators will always have the opportunity to contact the responsible CRA in case of any medical questions or concerns. If deemed necessary, the CRA will immediately reach out to the appropriate persons at LEO Pharma for medical support and further clarification.

Participation in clinical trials may currently be associated with increased risks and challenges due to the COVID-19 pandemic caused by SARS-CoV-2. Based on non-clinical studies, LEO 152020 is considered a mild immunomodulatory compound and its mechanism of action is not believed to present a risk of a decreased antiviral immunity in subjects infected by COVID-19. In addition, LEO 152020 is not believed to increase the susceptibility of the subject to contract COVID-19 or other infections. However, a risk of exposure to infected people cannot be excluded as the subject may enter public areas (e.g. commute to the trial site) and have human contacts (e.g. with the site staff). Therefore, risks must appropriately be assessed, and mitigation measures taken to protect the subject and site staff and to ensure the integrity of the trial data.

Both EMA and FDA as well as national health authorities in Europe have issued new guidelines aiming at providing recommendations for conduct of clinical trials during the COVID-19 pandemic [21-23] . Given the potential for the pandemic situation to relapse in relation to spread of COVID-19 in the future, special attention will be paid to protecting subjects and site staff involved in the trial against infection with SARS-CoV-2.

During the trial, the investigators will be trusted to take appropriate action to ensure individual subject safety according to the recommendations and preventive measures issued by their local authorities.

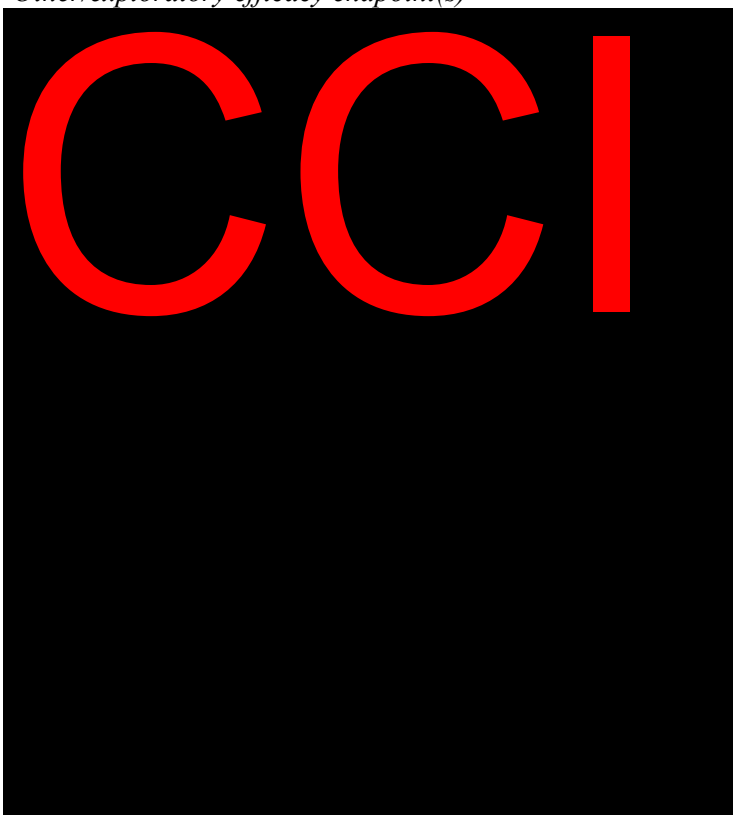
Mitigation measures that are currently planned to be implemented in this clinical trial in case of an escalation of pandemic situation are detailed in a separate document ("Mitigation Measures due to COVID-19 Pandemic"), that will be part of the submission package send to the relevant Ethics Committee and the Competent Regulatory Authority for approval.

As a result of the ongoing risk evaluation, further mitigation measures may come into force, resulting in an update of the above-mentioned document. If additional mitigation measures require approval, a substantial amendment will be submitted to the relevant Ethics Committee and the Competent Regulatory Authority and will not be implemented until approved. Exceptions to this are amendments made to eliminate immediate hazards to the patients ("urgent safety measures"). In this case the relevant Ethics Committee and the Competent Regulatory Authority will be notified about changes as soon as possible considering national and local circumstances.

6 Trial objectives and endpoints

The primary objective of EXP-2177 will be to evaluate the efficacy of LEO 152020 compared with placebo in patients with CholU. The choice of efficacy as the primary objective is supported by the completion of a first in man Phase 1 study demonstrating the safety of LEO 152020 at the proposed dosage. The secondary objective of this trial will be to evaluate the safety and tolerability of LEO 152020 compared with placebo in patients with CholU.

Panel 3: Objectives and endpoints

Objectives	Endpoints
Primary objective	
To explore the efficacy of LEO 152020 compared with placebo in patients with CholU.	Time frame: baseline of each treatment period to end of each treatment period *Primary efficacy endpoint* • Change from baseline in post-provocation Urticaria Activity Score (UASprovo) *Other/exploratory efficacy endpoint(s)* 
Secondary objective(s)	
To evaluate the safety of LEO 152020 compared with placebo in patients with CholU.	*Secondary endpoint* • Number of treatment emergent adverse events (TEAE) per subject. Time frame: start treatment period to 3 days after end treatment period

Objectives	Endpoints
Other/exploratory objectives	
To explore the expression of biomarkers of LEO 152020 compared with placebo in patients with CholU.	*Other/exploratory endpoint(s)* CCI
To explore the pharmacokinetics of LEO 152020 in patients with CholU.	*Other/exploratory endpoint(s)* CCI

Abbreviations: CholU - cholinerge urticaria, UASprovo – post-provocation Urticaria Activity Score, CholUAS7 - Cholinergic Urticaria Activity Score, UCT - urticaria control test, DLQI - dermatological quality of life index, CholU-QoL - cholinergic urticaria quality of life questionnaire, histamine SPT – histamine skin prick testing, VAS - visual analogue scale

7 Trial design

7.1 Overall trial design

EXP-2177 is a phase 2a, randomised, double-blind, placebo-controlled, multi-centre, cross-over trial conducted in Germany. The cross-over trial design is considered optimal to ensure clear evaluation of the drug effects, including safety and efficacy. Subjects will be randomised, stratified by site to one of two treatment sequences:

- Sequence 1) LEO 152020 CCI during treatment period A and placebo CCI during treatment period B,
- Sequence 2) Placebo CCI during treatment period A and LEO 152020 CCI during treatment period B.

Each treatment period will last 7 days. The placebo will serve as reference in evaluating efficacy and safety of LEO 152020. The cross-over trial design minimizes the sample size needed for the primary endpoint.

The trial will consist of three distinct parts as outlined below:

- Screening phase, day -21 to day -1: Duration of up to 3 weeks in which patients who have given informed consent are assessed for study eligibility. Subjects will have an initial wash-out period from H1 histamines of 7 days (day -7 to -1).
- Treatment phase:
  - Treatment period A:

    At visit 2 (randomisation; baseline of treatment period A) following confirmation of subject's eligibility, baseline assessments will be conducted, and subjects will be randomised. Subjects will start the first treatment period (LEO 152020 CCI or Placebo CCI) of 7 days at visit 2, first dose on site, preferably in the CCI and last dose on CCI of visit 3 at the site.
  - Washout period of 7 ± 1 days
  - Treatment period B:

    After confirmation of eligibility, subjects will start the second treatment period (Placebo CCI or LEO 152020 CCI) of 7 days at visit 4/4a (baseline of treatment period B), first dose on site at visit 4/4a, preferably in the CCI and last dose on CCI of visit 5 at the site.
- Safety follow-up: Safety assessments will be performed 3 days after last IMP dose.

Each part is associated with evaluations and procedures that must be performed at specific time points as described in the following sections and Panel 2.

If necessary, an unscheduled visit can be performed at any time and for any reason at the discretion of the investigator. Assessments to be performed during an unscheduled visit will depend on the reason why this visit is performed.

7.1.1 Screening phase (Days -21 (-7) to -1)

During the screening phase, the subjects' eligibility to enter the clinical trial will be confirmed. At visit 1 (screening) laboratory samples will be collected and electrocardiogram (ECG) measurements will be performed. A standardized physical exercise provocation (pulse-controlled ergometry [PCE]) for UASprovo assessment will be performed if the subjects had not a prior provocation test within the last 6 months. In case the subject fails to meet the inclusion threshold of the UASprovo, they are allowed one additional attempt after at least 7 days. In general, there should be at least 7 days between provocation tests including between screening provocation test and visit 2 provocation test.

At the latest, subjects will be provided with a diary 7 days prior to the baseline visit (Visit 2) and will be instructed to complete assessments for the CholUAS7 on a daily basis. Subjects will have to stop treatment with systemic H1 antihistamines and/or systemic drugs with antihistamine properties (if applicable) at the start of the initial washout period (day -7 to -1). Application of topical antihistamines for the treatment of concomitant allergies is allowed to be continued, if applied in the standard prescribed dose. All procedures will be performed as specified in Panel 2.

7.1.2 Treatment phase (Visit 2 (Day 1) to Visit 5)

The treatment phase comprises the randomisation visit, and two subsequent treatment periods separated by a 7-day wash-out period. At the start of the treatment phase, subjects will be randomised at visit 2 (day 1, baseline treatment period A) to either LEO 152020 CCI or placebo in treatment period A in a 1:1 manner. Subjects will then receive the opposite treatment (Placebo or LEO 152020 CCI) in treatment period B.

Treatment period A

7.1.2.1 Visit 2 (Day 1, Randomisation) = Baseline for treatment period A

Inclusion/Exclusion criteria will need to be confirmed, in particular the UASprovo assessment and the check of subject's diary to confirm compliance with trial instructions. After confirmation of the eligibility visit 2 assessments as specified in Panel 2 and Panel 6 (sequence of assessments) will be performed. Subjects will be randomised and administer first

dose of IMP of day 1 at site, preferably in the CCI After CCI minutes ECG recording and PK sampling will be conducted.

7.1.2.2 Visit 3 (Day 8, -1 to +3)

Subjects will take the last dose of IMP in treatment period A in the CCI of visit 3 at site. Before IMP intake PK sampling will be performed. CCI minutes after IMP administration ECG recordings and further PK sampling will be conducted. Other trial assessments will be performed as specified in Panel 2 and Panel 6. IMP will be returned, and the diary will be checked.

Treatment period B

7.1.2.3 Visit 4 (Day 15 ± 1)/ Visit 4a (Day 22 ±1) = Baseline for treatment period B

After a wash out period of 7 ± 1 days, subjects will be tested for eligibility for start of treatment period B. Specific procedures will be performed as detailed in Panel 2 and Panel 6. The histamine SPT and UASprovo should be performed first before intake of first IMP for treatment period B. Subjects who fail to demonstrate a UASprovo ≥ 3 (with a minimum wheal score of ≥ 1 and minimum itch score of ≥ 1) will be required to attend an additional visit (visit 4a) 7±1 day later. All further procedures planned for V4 will only be conducted if the subject is eligible for treatment period B. In case visit 4a has to be scheduled, some procedures of the visit 4 as specified in Panel 2 will be cancelled. At V4a the UASprovo will be assessed again. If subjects fail to demonstrate a UASprovo ≥ 3 (with a minimum wheal score of ≥ 1 and minimum itch score of ≥ 1), they will be terminated from the trial and an early termination visit will be performed.

For eligible subjects all remaining procedures as specified in Panel 2 will conducted and IMP for treatment phase B will be distributed. Subjects will administer first dose of IMP on visit 4 or visit 4a, respectively, at site, preferably in the CCI

7.1.2.4 Visit 5 (Baseline for treatment period B + 7 Days, -1 to +3)

Subjects will take the last dose of IMP in treatment period B in the CCI of visit 5 at site. Before IMP intake, PK sampling will be performed. CCI minutes after IMP administration ECG recordings and further PK sampling will be performed. Other trial assessments will be performed as specified in Panel 2 and Panel 6. IMP will be returned, and the diary will be returned and checked.

7.1.3 Visit 6 - Safety Follow-up (Visit 5 +3 (+4) Days) / End of Trial

A safety follow-up visit will be performed as end of study visit 3 days after last dose of IMP. Assessments will be conducted as detailed in Panel 2. Subjects who discontinue the study early should be requested to return for an early termination / end of treatment visit (see also Section 10.3) in addition at the time of the decision to withdraw from the study.

Any serious adverse events (SAEs) will be followed up as specified in Section 13.7.

7.2 Number of subjects needed

A total of 28 subjects will be randomised in the trial. An expected screening failure of 10% and an expected attrition rate of 10% is assumed.

This trial will be conducted at approximately 3-6 sites in Germany.

The statistical power considerations for this sample size are described in Section 14.1.

7.3 End of trial definition

A subject is considered to have completed the trial if they have completed all periods of the trial including the safety follow-up visit (visit 6).

The end of the trial is defined as the date of the last visit of the last subject in the trial.

Final collection of data for the primary endpoint occurs at visit 5.

8 Trial population

8.1 Subject eligibility

The investigator should only include subjects who meet all eligibility criteria, are not put at undue risk by participating in the trial and can be expected to comply with the protocol.

The subject's eligibility for the clinical trial must be verified according to the inclusion and exclusion criteria at visits specified in Panel 2. It will be recorded in the electronic case report form (eCRF) if the subject has met all the inclusion criteria and none of the exclusion criteria.

Any implementation of national requirements/law for the subject's participation in the clinical trial will be ensured and described in submission documentation to regulatory authorities and IECs, as applicable.

8.2 Inclusion criteria

For inclusion into this trial, subjects must fulfil all of the following criteria:

1. Signed and dated informed consent has been obtained prior to any protocol-related procedures.

2. Subject with a history of CholU diagnosis for ≥ 6 months (based on medical records).

3. Subject has active and uncontrolled CholU disease at the time of screening and randomisation, as defined by the following:

    a. Urticaria control test (UCT) < 12 at screening

    b. UASprovo ≥ 3 (with a minimum wheal score of ≥ 1 and minimum itch score of ≥ 1) at screening* and randomisation

        i. *Screening provocation test is optional if patients had a prior provocation test that met threshold within 6 months of day 1 (visit 2)

4. Age 18 or older

5. Patients must not have more than one missing diary entry in the 7 days prior to randomisation.

6. Recent history (within 6 months of screening) with documented inadequate response to standard dose as to marketing authorization of H1 antihistamines

7. Female subjects of childbearing potential* must use a double contraception i.e. a highly effective** plus a barrier*** form of birth control throughout the trial from screening until follow-up visit.

    * A woman of childbearing potential (WOCBP) is defined as a female subject aged ≥12 years old *or* a younger girl who, at the discretion of the investigator, is deemed to be of reproductive potential. A woman is defined as not being of childbearing potential if she is postmenopausal (at least 12 months with no menses without an alternative medical cause prior to screening), or surgically sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).

**A highly effective method of birth control is defined as one which results in a low failure rate (less than 1% per year) such as bilateral tubal occlusion, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), sexual abstinence (when this is in line with the preferred and usual life style of the subject and not just being without a current partner), vasectomised partner (given that the subject is monogamous and that the vasectomised partner has received medical assessment of the surgical success).

*** barrier method such as male condom with spermicide, female condom with spermicide, over-the-counter sponge with spermicide, cervical cap with spermicide, diaphragm with spermicide.

8. Male subjects with a female partner of childbearing potential must use adequate double contraceptive methods (barrier such as male condom with spermicide, female condom with spermicide, over-the-counter sponge with spermicide, cervical cap with spermicide, diaphragm with spermicide in conjunction with a highly effective form of female contraception for the partner), from randomisation to follow-up visit.

8.3 Exclusion criteria

Subjects must not enter the trial if they fulfil any of the following exclusion criteria:

1. Other clearly dominating forms* of urticaria as aetiology for wheal and flare type reactions, including:
   a. Chronic spontaneous urticaria
   b. Inducible urticaria: urticaria factitia / symptomatic dermographism, cold-, heat-, solar-, pressure-, vibratory-, aquagenic-, or contact-urticaria

*These diseases are allowed as comorbidities, if cholinergic urticaria is the dominating form of chronic urticaria

2. Clinically significant infection within 4 weeks prior to randomisation that may compromise the safety of the subject
3. History of lymphoproliferative disease or any known malignancy or history of malignancy (except for treated non-melanoma skin cancer or treated cervical carcinoma in situ) within the past 5 years

4. Risk factors for Torsades de Pointe including:
    a. Uncorrected hypokalemia, hypocalcemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia
    b. (Congenital) long QT syndrome or family history of idiopathic sudden death
    c. Concomitant medication(s) with a known risk of Torsades de Pointe that cannot be discontinued or replaced by safe alternative medication
    d. Other cardiac arrhythmia risk factors at the discretion of the investigator
5. Use of concomitant medication for which QT prolongation is a known side effect and which cannot be discontinued or replaced by (a) safe alternative medication(s) within 5 half-lives prior to screening
6. Resting QTcF (average of a triplicate measurement) < 300 msec or > 450 msec at screening
7. Known history of ventricular arrhythmias
8. Second- and third-degree atrioventricular block
9. Subjects with signs of renal impairment as determined estimated glomerular filtration rate (eGFR) levels below 90 mL/min at screening.
10. Subjects with signs of hepatic impairment as determined by abnormal liver function tests, defined as total bilirubin, aspartate aminotransferase or alanine aminotransferase >1.5 x the upper limit of normal (ULN) range, at screening.
11. Infection with human immunodeficiency virus (HIV)
12. Presence of hepatitis B or C infection, defined as: Positive hepatitis B surface antigen (HBsAg), or hepatitis B core antibody (anti-HBc), or hepatitis C virus antibody serology at screening. Subjects with positive anti-HBs are eligible provided that they have a negative HBsAg *and* negative HBc (blood pattern in vaccinated subjects).
13. Subjects with confirmed active infection with SARS-CoV-2 AND related COVID-19 symptoms, which at the discretion of the investigator will jeopardize the safety of the subject or the integrity of the data collected. Additionally, any local requirements must be followed.
14. Any medication known to chronically alter drug absorption or elimination processes within 30 days prior to the first dose of IMP.
15. Systemic immunosuppressive medications (e.g. Methotrexate, Cyclosporine, Azathioprine) within 4 weeks prior to screening and throughout the trial.

16. Systemic corticosteroids within 4 weeks prior to screening and throughout the trial (Note: Inhaled or intranasal steroids equivalent to doses up to 1 mg prednisone daily is allowed).
17. Drugs which are known inhibitors of the P-gp and BCRP transporters as well as the strong OAT3 inhibitor probenecid within 1 weeks prior to randomisation or 5 half-lives (whichever is longer) and throughout the trial.
18. Systemic drugs (e.g. oral drug) with antihistamine properties including H1 antihistamines and some antidepressants (e.g. tricyclic antidepressants) and H2 antihistamines 1 week prior to randomisation and throughout the trial. However, topical antihistamines in the form of nasal spray and eyedrops are allowed in the standard prescribed dose.
19. Use of tanning beds or phototherapy (narrow band ultraviolet B [NBUVB], ultraviolet B [UVB], ultraviolet A1 [UVA1], psoralen + ultraviolet A [PUVA]) within 4 weeks of screening and throughout the trial.
20. Known or suspected hypersensitivity to any component(s) of the IMP or to a drug of a similar chemical class.
21. Known hypersensitivity to iodine
22. Current participation in any other interventional clinical trial.
23. Treatment with any non-marketed drug substance (that is, an agent which has not yet been made available for clinical use following registration) within 5 half-lives or last 3 months, whichever is longer.
24. Previously randomised in this clinical trial.
25. History of chronic alcohol or drug abuse within 12 months prior to screening, or any condition associated with poor compliance as judged by the investigator.
26. Employees of the trial site or any other individuals directly involved with the planning or conduct of the trial, or immediate family members of such individuals.
27. Subjects who are legally institutionalised.
28. Female subject who are pregnant or lactating.
29. Any unstable medical, surgical, psychiatric, or additional physical disorder* at any time during the trial and which according to investigator's opinion could:
    - Affect subject safety and well-being or put the subject at risk because of their participation in the trial.

- Influence the findings of the trial.
- Impede the subject's ability to complete the trial.

*Examples include but are not limited to cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, immunological, and psychiatric disorders and major physical impairment.

30. Any clinically significant abnormal finding at screening and/or baseline which according to investigator's opinion may:

    - Affect subject safety and well-being or put the subject at risk because of their participation in the trial.
    - Influence the results of the trial.
    - Influence the subject's ability to complete the trial.

    The abnormal finding must be clinically significant and observed during the screening period. Examples include abnormal findings in physical examination, vital signs, electrocardiogram (ECG) (based on the central ECG report provided by the ECG vendor), haematology, clinical chemistry, or urinalysis.

8.4 Screening and screening failures

Subject identification number

Trial participation begins once written informed consent is obtained. Refer to Appendix 3B for details on the informed consent process. Once informed consent is obtained, subjects will be assigned to ascending subject identification numbers (subject ID) in the order of their appearance at Screening and the screening evaluations to assess eligibility criteria may begin. The subject ID will be automatically generated by the eCRF system. The generation and composition of the subject ID will be described in the Completion Guide for the eCRF. The date of first screening activity could be on the same day or a later date than the informed consent was signed. The subject ID will be used to identify the subject during the screening process and throughout trial participation, if applicable. Subjects who have given written informed consent to participate in the trial and who have been assigned a subject ID are considered 'screened' subjects. The investigator will maintain a log of all consented subjects at the trial site (subject identification list) including subjects who are not randomised in the trial/ treatment assigned. This log will include each subject's identity, date of consent and corresponding subject ID so that any subject may be identified if required for any reason. The date of screening and the status (screening failure or randomised) should also be documented.

The log must not be copied or retained by LEO Pharma. All subjects who signed the informed consent form must be entered into the eCRF.

In addition, the investigator will maintain a log of all subjects considered for screening, whether they have provided written informed consent or not (pre-screening log). This log will be anonymous and will include the reason(s) for not entering the trial, if applicable, or the allocated subject ID.

Screening failures
Screen failures are defined as subjects who consent to participate in the trial but are not subsequently [randomly] assigned to trial treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. As a minimum, the following data will be collected in the eCRF

for screen failures:

- Date of informed consent(s).
- Demographics (age [year of birth], sex, race).
- Reason for screen failure.
  - Failure to meet eligibility criteria for randomisation
- Date of screen failure.
- Any adverse events (AEs) and serious AEs (SAEs).
- End of trial form (including other reasons for non-participation, if applicable)

In case of any SAEs, these must be followed-up as described in Section 13.7.

Re-screening of screening failures is allowed once if deemed appropriate by the investigator e.g. in case of highly abnormal and obviously wrong laboratory values, due to logistical reasons or once due to missed UASprovo threshold. At re-screening a new subject ID will be assigned.

9 Treatments

9.1 Trial product description

Panel 4: Identification of investigational medicinal products

Investigational medicinal product	Dosage form	Active ingredient and concentration	Manufacturer responsible for batch release
LEO 152020 CCI mg film-coated tablets	Film coated tablet	LEO 152020 CCI [redacted]	LEO Pharma A/S,
Placebo film-coated tablet	Film coated tablet	Not applicable	LEO Pharma A/S,

9.2 Administration of investigational medicinal product

LEO 152020 or placebo will be administered orally for 7 days each during treatment period A and B according to the following dosing regimens:

- LEO 152020 CCI [redacted]
- Placebo CCI [redacted]

The subject will be asked to take CCI tablets orally: CCI [redacted] CCI [redacted] The IMP will be dispensed to the subject according to the schedule of trial procedures (Panel 2). During the respective treatment period, the subject will be asked to self-administer the IMP. Doses of IMP will be taken at the site or at the subject's home as explained below.

First administration in each treatment period (A and B) will take place during patient's visits at site, preferably in the CCI [redacted] If visits are performed in the afternoon, the next following dose need to be at least 9 hours after the previous dose. If this is not possible on the same days, the next administration will be the CCI [redacted] dose on the next day. On the days planned for the study visits (visit 3 and visit 5, respectively), the subject must not take the CCI [redacted] dose at home. The last administration in each treatment period (A and B) will be done on site during these visits.

As the administration of the IMP on site should be done under fasting conditions, subjects should already be instructed at their screening visit to avoid food intake 2 hours prior to the scheduled IMP administration on site (visit 2 to visit 5).

The remaining doses will be administered by subjects themselves at home without regard to dietary intake (i.e. fasting or fed condition).

Administration of the IMP at the site

Visits should be scheduled at times to make the fasting requirements and minimum time of 9 hours between consecutive doses of IMP feasible for the subject. At each visit, before the subject takes the IMP, the trial staff should clarify with the subject when they took their last dose of IMP before the visit and when they had their last food intake.

- If the subject took their last dose of IMP more than 6 hours prior to the visit, they may take the planned dose of IMP at the clinic.

- If the subject took what would be considered their CCI dose of IMP less than 6 hours prior to the visit the next CCI this should be documented as a medication error (Section 13.6.2). In this case, the subject may take the planned dose of IMP at the clinic, unless considered contraindicated by the investigator.

- If subjects have food intake less than 2 hours before the scheduled IMP administration on site, they have to wait a correspondingly long time before taking the IMP. The next following food intake should only be done at least 1 hour after the IMP administration.

- If the subject took a CCI dose of IMP in error before coming to the clinic for their visit, the visit should be rescheduled within 3 days (ensuring that the subject has sufficient IMP to continue with the treatment for this period).

Administration of the IMP at the subject's home

When taking the IMP at their home, the subject is recommended to take the CCI dose of IMP just after waking up. In the CCI the subject is recommended to take the IMP just before going to bed. If this is inconvenient, the subject may take the IMP at other times during the day as long as the minimum time of 9 hours between 2 consecutive doses of IMP can be met.

When taking the IMP at their home, subjects may take the IMP without regards to dietary intake (i.e. fasting or fed condition).

Subjects will be asked to record the date and time of each IMP intake. This will allow monitoring of treatment compliance (Section 9.8.4) and whether consecutive doses were taken at least C hours apart.

In case the subject forgets to take a dose of IMP or misses a visit at the clinic, the subject should proceed as follows:

- If there is a minimum time of 9 hours to the next planned dose of IMP, the subject should take the forgotten dose of IMP as soon as the subject becomes aware.

- If there are less than 9 hours to the next planned dose of IMP, the subject should skip the forgotten dose of IMP and wait until the next planned dose of IMP. In such case, the subject should record the missed dose of IMP as forgotten.

Subjects will receive the IMP for treatment period A at visit 2 and will return all unused tablets and the packaging at visit 3. For treatment period B the IMP will be dispensed at visit 4 (or visit 4a, if start of treatment period B was delayed by 7 days) and subjects have to return all unused tablets and the packaging at visit 5. For details about dispensing visits please refer also the schedule of trial procedures (Section 4). At each dispensing visit site staff will dispense IMP with the appropriate kit number for the subject (for details see also Section 9.3). The date of dispensation and the kit number of the IMP will be collected in the eCRF.

Provisions for overdose

The risk of accidental overdose of clinical consequence on QT prolongation is considered low as it would involve intake of an unlikely large dose of IMP at once: CCI mg in a single dose*, equivalent to C tablets of active IMP (*based on results of the first in human trial with LEO 152020, reference IB [8]). In the unlikely event of an overdose, there is a small risk of QT prolongation (complication and no visible sign). To minimize the risk of accidental overdose, it will be explained to the subject at the clinic and in an instruction for use for the subject to take home how the subject should take the IMP. Date and time of IMP intake recorded by the trial staff in the eCRF (for doses of IMP taken at the clinic) and recorded by the subject in the diary (for doses of IMP taken at the subject's home), as well as review of treatment compliance (Section 9.8.4) and IMP accountability (Section 9.8.3) may all be used to detect any medication error, including accidental overdose (Section 13.6.2).

LEO Pharma does not recommend any specific treatment in relation to overdose. If needed, it will be at the discretion of the investigator to treat any accidental overdose appropriately

9.3 Treatment assignment

Treatment assignment will be pre-planned according to a computer-generated randomisation schedule. This **randomisation schedule** randomly allocates subjects who have been found to comply with all the inclusion criteria and not to violate any of the exclusion criteria on day 1 (visit 2) in a 1:1 ratio to one of the two treatment sequences. Treatment will start either with LEO 152020 CCI or with Placebo in treatment period A and will continue with the opposite treatment (Placebo or LEO 152020 CCI) in treatment period B.

The blinded products are labelled with **product codes** e.g. “W” or “Z” and a unique kit number. The randomisation number will assign the subject in each treatment period to one of the two products labelled with the product codes. For each site a complete randomisation schedule will be generated, such that each site could randomise 28 subjects. The randomisation number and the kit numbers have to be documented in the CRF.

Visit 2 (Day 1) and Visit 4 (or 4a)

At day 1 eligible subjects will receive the next available **randomisation numbe**r at the trial site, which assigns the subject to one of the two treatment sequences. The study personnel responsible for dispensing of products will dispense for the first treatment period one IMP kit labelled with the product code as indicated on the randomisation list for this randomisation number.

At the next dispensing visit delegated site staff will dispense an IMP kit with the product code for the next treatment period as indicated in the randomisation schedule for subject’s randomisation number.

At visit 2 and visit 4 (or 4a, respectively), the unique kit number dispensed to the subject has to be documented in the eCRF and the subject’s record.

Each trial site will be supplied with sufficient IMP for the clinical trial on an ongoing basis.

The randomisation schedules will be generated by a non-blinded statistician. The non-blinded statistician will be used only for generating the randomisation list. He/she will be excluded from other study operations. The code lists will be inaccessible to staff involved with the conduct and administration of the clinical trial until the clinical trial is un-blinded.

The randomisation code number will be a 3-digit code.

9.3.1 Blinding

The trial is conducted as a double-blind trial. Subject, investigator, and staff involved in the data analysis and reporting of the results will be blinded to the planned and actual treatment from randomisation to the formal unblinding of the trial. Distribution of the products must be performed by site staff not involved in assessments of efficacy or safety parameters. Blinding will minimise ascertainment bias due to getting knowledge of the treatment.

LEO 152020 film-coated tablet ([redacted] mg) and placebo film-coated tablet have been designed to have the same size and colour so that active and placebo treatments look and feel identical.

The packaging of LEO 152020 film-coated tablet ([redacted] mg) and placebo film-coated tablet also contains no direct evidence of their identity. It is not considered possible to differentiate between the IMPs solely by sensory evaluation. The products are labelled with product codes at the contract manufacturing organisation (CMO) but it will not be disclosed which product code indicates LEO 152020 or placebo until the clinical trial is un-blinded.

9.3.2 Emergency unblinding of individual subject treatment

While the safety of a subject always comes first, it is still important to carefully consider if unblinding is necessary to ensure a subject's safety. An emergency unblinding request can be made by the investigators, health care professionals (HCPs) who are not members of the trial staff, or authorised LEO Pharma personnel.

Provisions are in place for 24-hour emergency unblinding of individual subject treatment. If emergency unblinding is required, the investigator or delegated site staff can directly contact the emergency unblinding CRO via a corresponding local emergency unblinding telephone number, that can be found in the Investigator Site File (ISF).

The investigator or delegated site staff will need to provide the trial ID, the subject ID and the randomisation code number of the subject to the emergency unblinding CRO who will immediately reveal the individual treatment allocation.

For a requester who is not a member of the site staff (e.g. a physician in an emergency room), the local contact number for the emergency unblinding CRO will be provided on the subject card (Appendix 3B) to be used if the investigator or delegated site staff cannot be reached. Like the investigator or delegated site staff, the requester need to provide the trial ID, the

subject ID and the randomisation code number to the emergency unblinding CRO, that will immediately reveal the individual treatment allocation.

The emergency unblinding CRO will clarify that the requester requires immediate unblinding without further medical consultation.

Unblinding should only be done in case of an emergency and when it is essential for effective treatment of the subject. Most often, trial drug discontinuation and knowledge of the possible treatment assignments are sufficient to treat the subject. The Sponsor is to be informed immediately about any unblinding event.

Documentation of any unblinding should include the name of the trial personnel performing the unblinding, the date of the unblinding and the reasons that led to unblinding. It has to be reported on the blind break form filed in the Investigators site file. In addition, AEs or SAEs related to the unblinding have to be reported appropriately.

LEO Pharma Global Safety will receive a set of emergency envelopes, including the identity of the product codes for potential unblinding for regulatory purpose.

9.4 Background treatment

Not applicable

9.5 Rescue treatment

Not applicable

9.6 Concomitant medication and concurrent procedures

Any medication or vaccine that the subject receives from 28 days prior to screening through safety follow-up must be recorded in the subject's medical record and the eCRF along with details such as:

- Medication name or therapy (generic or brand name).
- Whether the medication or therapy is a rescue medication for the indication.
- Indication (e.g. concomitant diagnosis, prophylaxis).

- Start and stop date of administration (it will also be recorded if the medication is ongoing).
- Dosage information, including dose per administration, unit, and frequency.
- Route of administration ([oral, topical, subcutaneous, transdermal, intraocular, intramuscular, respiratory (inhalation), intralesional, intraperitoneal, nasal, vaginal, rectal, intravenous, or other (if other, a specification must be provided)). For topical treatments, the dosage form (cream, lotion, ointment, other) will also be recorded.

For vaccines the following details should be recorded:

- Type of vaccine (brand name)
- Indication (e.g. COVID-19 vaccination)
- Location of injection (e.g. left upper arm)
- Specify dose (dose x of y)
- Start and stop date (start date = stop date)

Similarly, any concurrent procedure must also be recorded in the subject's medical record and the eCRF. The following details will be recorded: procedure name (including anatomical area, if relevant), indication, and start and stop date (it will also be recorded if the procedure is ongoing).

The investigator must collect the information from each subject (WOCBP and males with partners of childbearing potential) which contraception is used with their partners. This information should be collected from every subject at those visits when a pregnancy test is performed (but from ALL subjects as specified above). This information should only be documented in the source documents to confirm inclusion criterion 7 and 8.

Investigators may prescribe concomitant medications or treatments to provide adequate supportive care as deemed necessary, except for medications listed in Section 9.7. The sponsor's medical expert should be contacted if there are any questions regarding concomitant or prior therapy.

9.7 Prohibited medication(s) and procedures

The medications and/or procedures listed in Panel 5 are prohibited during the trial as specified below.

Panel 5: Prohibited medication(s) and/or procedure(s)

Medication	**Prohibited from**	**Prohibited to**
Systemic immunosuppressive medications (e.g. Methotrexate, Cyclosporine, Azathioprine)	4 weeks prior to screening	Safety follow-up
Biologic medications (e.g. omalizumab, dupilumab)	5 half-lives prior to screening	Safety follow-up
Systemic corticosteroids	4 weeks prior to screening (Note: Inhaled or intranasal steroids equivalent to doses up to 1 mg prednisone daily is allowed)	Safety follow-up
Systemic H1 antihistamines with no risk for QT prolongation*	1 week prior to randomisation	Safety follow-up
Systemic H1 antihistamines with risk for QT prolongation*	1 week prior to randomisation or 5 half-lives (whichever is longer)	Safety follow-up
H2 antihistamines	1 week prior to randomisation	Safety follow-up
Drugs with antihistamine properties including some antidepressants (e.g. tricyclic antidepressants)	1 week prior to randomisation	Safety follow-up
Drugs with a known effect on the QT interval	1 week prior to randomisation or 5 half-lives (whichever is longer)	Safety follow-up
Drugs which are known inhibitors of the P-gp and BCRP transporters**	1 week prior to randomisation or 5 half-lives (whichever is longer)	Safety follow-up
Probenecid (strong OAT3 inhibitor)	1 week prior to randomisation or 5 half-lives (whichever is longer)	Safety follow-up

* The application of topical antihistamines (e.g. nasal sprays or eyedrops) for the treatment of concomitant allergies (e.g. allergic rhinitis or hay fever) in the standard prescribed dose is allowed to be continued during the entire trial, if applicable.

**See Appendix 4 as examples of BCRP or P-gp transporters.

In case any prohibited treatments are used during the trial, they must be recorded as concomitant medication and reported as protocol deviation by the CRA.

In case any prohibited medication with known effect on the QT interval or known inhibitors of the P-gp and BCRP transporters and the strong OAT3 (organic anion transporter 3) inhibitor probenecid were used, the medical monitor must be immediately notified and an early termination visit for the subject should be considered.

9.7.1 Other restrictions

The following restrictions must be adhered to during the trial and for the following time periods:

Procedure	**Prohibited from**	**Prohibited to**
Use of tanning beds or phototherapy (narrow band ultraviolet B [NBUVB], ultraviolet B [UVB], ultraviolet A1 [UVA1], psoralen + ultraviolet A [PUVA])	Within 4 weeks of screening	Safety follow-up
Practices	**Prohibited from**	**Prohibited to**
Exposures likely to trigger a strong CholU flare (e.g. strenuous exercise, sauna)	24 hours prior to UASprovo	UASprovo

Non- adherence to these restrictions will be reported as protocol deviations.

9.8 Treatment logistics and accountability

9.8.1 Labelling and packaging of trial products

The IMP will be packaged in individually numbered kits.

The labelling of IMPs will be in accordance with Annex 13, local regulations and trial requirements. Label text will be translated into local language, as required.

For home-use, the subjects will receive instructions for use which will be translated into local language. These will be part of the subject's diary.

9.8.2 Storage of trial products

All LEO Pharma supplied IMPs must be stored in a secure and restricted area under the conditions specified on the label and remain in the original container until dispensed.

At the trial site and/or pharmacy at the trial site, the IMP must be stored below 25°C. The IMP must not be refrigerated nor frozen.

The temperature during storage at the trial site should be monitored by a calibrated, stationary, and continuously monitoring system. Minimum requirement is a calibrated min/max thermometer.

A temperature log must be kept documenting the storage within the right temperature interval. Storage facilities should be checked at least every working day.

At the subject's home, the IMP should be stored at room temperature below 25°C and should not be refrigerated or frozen.

9.8.3 Drug accountability

The investigator is fully responsible for the IMPs at the trial site and for maintaining adequate control of the IMPs and for documenting all transactions with them.

Dispensing of IMPs may be delegated, e.g., to a hospital pharmacy, as locally applicable.

Documentation of drug accountability must be kept of the IMPs dispensed to and returned by each individual subject randomised in the trial. This documentation must be available during monitoring visits and will be checked by the CRA to verify correct dispensing of the IMPs. Drug accountability information will be recorded for individual drug accountability per subjects as well as for the inventory status of all IMPs at the trial site on paper forms.

The subject will return unused IMPs (including packaging material) at the visits specified in the schedule of trial procedures (Section 4).

Returned trial product (unused IMPs (including packaging material)) can be stored at room temperature and must be stored separately from non-allocated trial product.

All [unused] IMPs (including packaging material) supplied by the CMO on behalf of LEO Pharma will be returned to the CMO. Prior to their return, the IMPs must be fully accounted for by the CRA with the help of site staff responsible for dispensing the IMPs. Accountability must be documented on drug accountability forms.

IMPs will be returned from the trial site to the CMO directly.

9.8.4 Treatment compliance

At visit 3 (end of treatment period A) and visit 5 (end of treatment period B) the subjects will be asked if they have used the IMPs as instructed, and the diary will be reviewed by site personnel. If a subject is found to be non-compliant during treatment period A, the investigator should remind the subject of the importance of following the instructions given, including taking the IMP as prescribed during dispensation visit (visit 4 or 4a, respectively). Compliance/non-compliance and the reason for it must be recorded in the eCRF.

Reporting in eCRF
The following data will be recorded in the eCRF:

- Did the subject comply with the IMP dosing schedule and instructions (yes, no); If no, the number of tablets not taken (including timepoints for missing intakes) and /or instructions which were not adhered to (e.g. dietary instructions, interval between doses) will be documented.
- Primary reason for non-compliance - subject forgot, lack of time, adverse event, other (if other, a specification should be provided).
- Total number of tablets taken per treatment period.

9.8.5 Trial product destruction

All unused and partly used wallets containing IMP must be returned to CMO for destruction. Completely empty wallets can be destroyed locally according to approved procedures and/or local requirements.

9.9 Provision for subject care following trial completion

In order to ensure appropriate treatment of the subjects after they have completed the trial, the subjects will be treated at the investigator’s discretion or referred to other physician(s) according to standard practice.

9.10 Reporting product complaints

Any defects or issues with the IMP including use errors and inadequate labelling must be reported to the Quality Department via Global Safety at LEO Pharma on the trial specific (paper) complaint form within 3 days of first knowledge.

Critical complaints (defined as any defect, issue, that has or potentially could have a serious impact on the subject [e.g. SAE]) must be reported to the Quality Department via Global Safety within 24 hours of knowledge.

Complaint forms should contain a detailed description of the defect, issue, including whether it led to an AE. (S)AEs which occur due to a defect or issue with the IMP will be reported by the investigator as described in Sections 13.3 and 13.4.

During the investigation of the product complaint, the IMP must be stored at labelled conditions unless otherwise instructed. The trial site will be notified whether the IMP needs to be returned for further investigation or may be destroyed.

Global Safety, LEO Pharma contact information for reporting product complaints:

E mail address: drug.safety@leo-pharma.com

Fax number: +45 69102468

10 Discontinuation and withdrawal

10.1 General principles

A subject may withdraw from the trial (prior to first dose or during any treatment period) or permanently discontinue trial treatment at any time if the subject, the investigator, or LEO Pharma considers that it is not in the subject's best interest to continue.

A subject who permanently discontinues IMP is a subject who, although they stop treatment with the IMP, agree to their follow up as described in Section 10.3. A subject who withdraws from the trial is a subject who stops treatment with the IMP and all further protocol defined trial activities. Early termination assessments to be conducted for both events are described in Section 10.3.

Subjects who withdraw from the trial after first dose and subjects who permanently discontinue IMP will not be replaced.

If a subject withdraws from the trial, they may request destruction of any samples taken and not tested, and the investigator must document this in the subject's medical record.

10.2 Reasons for permanent discontinuation of IMP

10.2.1 Reasons for permanent discontinuation of IMP

Subjects will permanently discontinue IMP in any of the treatment periods in the event of:

- Evidence of pregnancy.
- An AE that, in the opinion of the investigator or sponsor's medical expert, contraindicates further dosing.
- Initiation of prohibited medication which cannot be safely replaced by other non-prohibited medications.
- Clinically significant abnormal ECG parameter (e.g., QTcF >500 ms or change in QTcF from baseline (pre-dose ECG) > 60 ms).
- Symptomatic infection with SARS-CoV-2 that is likely to have an impact on efficacy or safety data (i.e., patients with a SARS-CoV-2 infection without or very mild symptoms

only (e.g., rhinitis or sore throat) might continue with the study at investigator's discretion and in accordance with the applicable local regulations).

- Other reasons, at the discretion of the investigator. If other, a specification should be provided.

It is not allowed to restart IMP treatment after discontinuation of IMP.

The primary reason for permanent discontinuation of IMP must be recorded in the medical records.

Data to be recorded in the eCRF
The primary reason for permanent discontinuation of IMP must also be recorded on the end of treatment form in the eCRF where the following options are available:

- Evidence of pregnancy.
- Adverse event (including but not limited to clinically significant abnormal ECG parameter (e.g., QTcF >500 ms or change in QTcF from baseline (pre-dose ECG) > 60 ms)
- Use of prohibited concomitant medication
- Withdrawal by subject
- Lost to follow-up
- Death
- Other reasons, at the discretion of the investigator.

If 'adverse event' or 'other' is selected, a specification must be provided in the eCRF.

If 'adverse event' is selected, the AE in question will be linked to the discontinuation of IMP.

If 'withdrawal by subject' is selected, it will be recorded whether the subject withdrew informed consent or not.

Discontinuation of IMP due to COVID-19 pandemic will be collected and specified in the 'Other' category.

10.3 Early termination assessments

Permanent discontinuation of IMP

Subjects who permanently discontinue IMP for any reason will be asked to attend an early termination visit as soon as possible after last administration of IMP **and** return to the trial site for an additional visit (safety follow-up visit) as indicated below. See the schedule of trial procedures (Section 4) for data to be collected at these visits. The investigator will review any AEs which will be followed up according to Section 13.7, if the subject agrees.

Subjects who permanently discontinue IMP will be asked to attend:

- Early termination visit (as soon as possible following the last administration of IMP, i.e. not more than 3 days after last IMP administration. If no early termination visit can be performed within this time frame, only the safety follow-up visit should be performed).

- Safety follow-up visit 3 (+4) days after last administration of IMP (in addition if early termination visit was performed within 3 days after last IMP administration).

Withdrawal from trial

Subjects who withdraw from the trial for any reason should attend a safety follow-up visit (see the schedule of trial procedures (Section 4) for data to be collected at safety follow-up visit). The investigator will review any AEs which will be followed up according to Section 13.7, if the subject agrees.

Details on data to be recorded in the eCRF for subjects who withdraw from the trial can be found in Section 11.8.

10.4 Lost to follow-up

A subject will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and if the trial site is not able to get in contact with the subject.

The following actions must be taken if a subject fails to return to the trial site for a required visit:

- The trial site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to continue in the trial.

- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject. These contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, they will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.

10.5 Criteria for the termination of the trial

The Sponsor, the signatory investigator, the IECs or regulatory authorities may decide to temporarily halt / suspend the trial, to stop the trial, parts of the trial or an investigational site at any time.

10.5.1 Termination of the whole trial

The discontinuation of the whole trial may be due but not limited to the following reasons:

- If risk-benefit ratio becomes unacceptable owing to, for example,
  - Safety findings from this trial (e.g. if (S)AEs occur with a frequency or intensity which significantly differ from the data reported in the IB, e.g. occurrence of severe QT-prolongation defined as QTcF > 500 ms or change in QTcF > 60 ms from baseline (pre-dose ECG) in more than 10% (i.e. more than 3 subjects) of the planned trial subjects)
  - Results of parallel clinical trials
  - Results of parallel animal studies (on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the trial conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.
- The development of the test product is discontinued, a market authorization is no longer intended, or the trial proves not to meet the expected goal.
- A regulatory authority demands that the trial be terminated.
- Revocation of Ethics Committee's favorable opinion or national regulatory authority's approval of the trial.
- Other important or unforeseen circumstances.

10.5.2 Termination of the trial at an individual trial site

The Sponsor has the right to close a single trial site at any time.

Conditions that may warrant termination of a trial site include, but are not limited to:

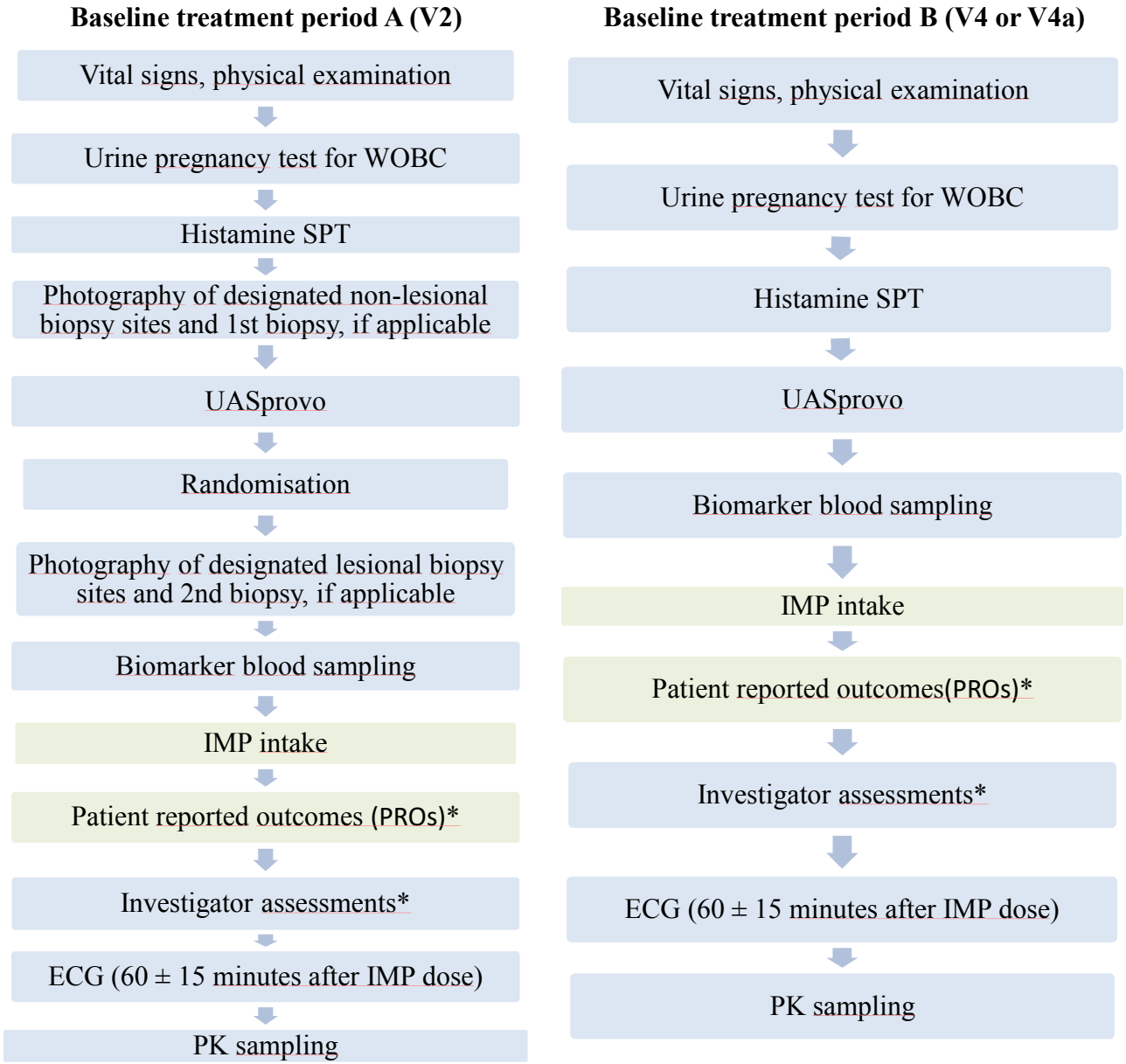
- The trial site fails to comply with the requirements of the protocol
- The trial site fails to comply with GCP standards
- The first subject fails to be recruited within a reasonable period after initiation of the trial site

11 Trial assessments and procedures

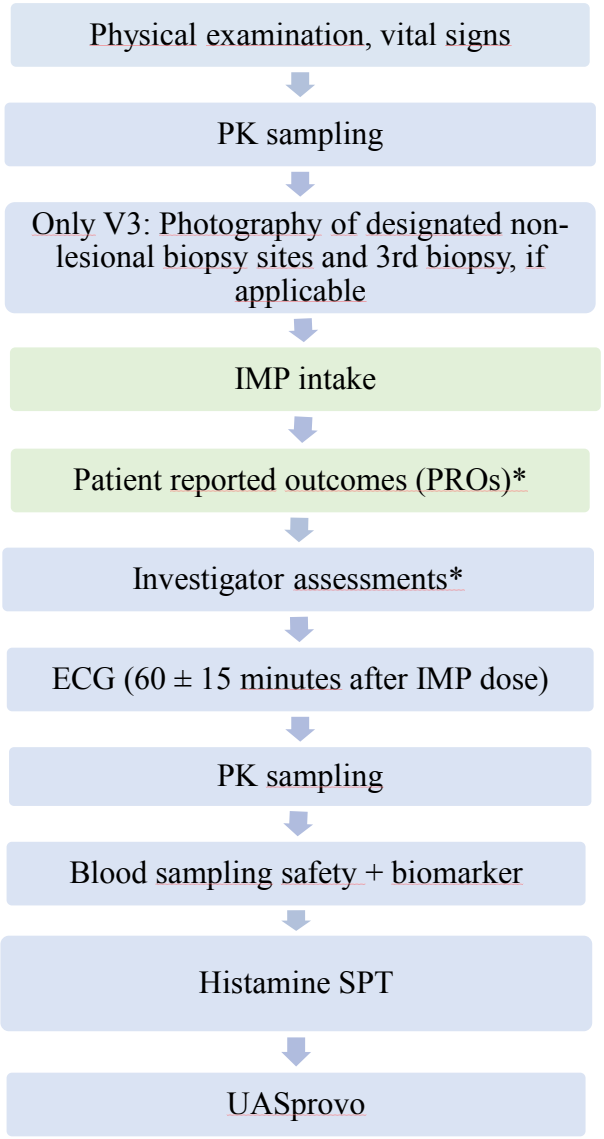
11.1 Overview

Evaluations to be done at each visit are shown in the schedule of trial procedures in Section 4. Refer to Section 7.1 for further details on the trial design. Assessments and procedures at each trial visit should be performed as shown in Panel 6:

Panel 6: Sequence of assessments



Visit 3 /Visit 5



*timing of assessments at the visit day is variable as long as PROs are performed prior to investigator's assessments

Subjects participating in the trial will be under careful supervision of a principal investigator who must be a dermatologist or allergist. Investigators must be experienced in treating cholinergic urticaria and have documented experience and/or training in use of the assessments required by the protocol and must be either a physician or certified physician's assistant.

AEs must be assessed by medically qualified personnel (Section 13.2).

11.2 Assessments performed only at screening/baseline

11.2.1 Demographics

The following demographic data will be recorded:

- Age (year of birth).
- Sex: female, male.
- Race: American Indian or Alaska native, Asian, Black or African American, native Hawaiian or other Pacific islander, White, other [requires a specification to be provided].
- Ethnic origin (self-reported by the subject): “Hispanic” or “Latino”, not “Hispanic or Latino”.

11.2.2 Medical history

Relevant medical history must be recorded:

- Skin disease history and history of CholU (to confirm the inclusion criteria): all past and current skin disease history should be collected; for each condition or diagnosis, the start date and stop date will be recorded (it will also be recorded if the diagnosis is ongoing).
- Other medical and surgical history including concurrent diagnoses within the previous 12 months. For each condition, diagnosis, or surgical procedure, the start date and stop date will be recorded (it will also be recorded if the condition, diagnosis, or surgical procedure is ongoing).

Relevant medical history also includes diseases which are specifically listed as exclusion criteria and diseases for which specific treatments are listed as exclusion criteria.

11.2.3 Height and weight

The subject’s height (without shoes) will be measured; the subject’s weight (in indoor clothing and without shoes) will be measured.

11.3 Efficacy assessments

11.3.1 Urticaria Activity Score post-provocation (UASprovo)

A pulse-controlled ergometry provocation test will be performed, and the investigator will assess the Urticaria Activity Score post-provocation (UASprovo). In addition, the time until sweating and whealing during the exercise will be determined.

The UASprovo will be performed according to the schedule of trial procedures (Section 4). Screening provocation test is optional if patients had a prior provocation test within 6 months of day 1 (visit 2). If subjects fail to meet inclusion threshold during screening provocation test, then they are allowed one additional screening attempt. There should be at least 7 days between provocation tests, including between screening provocation test and visit 2 provocation test. Subjects not meeting the inclusion criteria of a UASprovo ≥ 3 (with a minimum wheal score of ≥ 1 and minimum itch score of ≥ 1) at visit 2 must not be randomised.

Subjects who don't demonstrate UASprovo ≥ 3 (with a minimum wheal score of ≥ 1 and minimum itch score of ≥ 1) at Visit 4 may not progress to treatment period B and will be required to attend an additional study visit (visit 4a) 7±1 days later to repeat the provocation test. If at visit 4a subjects do not demonstrate a UASprovo ≥ 3, then they will be terminated from the trial.

UASprovo and the time until sweating and whealing will be recorded in the eCRF.

Pulse-controlled ergometry (PCE) provocation test

The pulse-controlled ergometry (PCE) provocation test is a standardized test for diagnosing and investigating CholU [26]. The test involves moderate physical exercise appropriate to the patient's age and general condition to the point of sweating and up to 15 minutes beyond. For this pulse-controlled incremental ergometry test, patients are seated on the bicycle ergometer and instructed to cycle in a pulse controlled manner, i.e. to speed up or slow down their pedalling speed to achieve an increase in pulse rate of 15 beats per minute every 5min to a final maximum increase of 90 beats per minute above the starting level.

Assessment of the Urticaria Activity Score

Starch-iodine powder will be applied to the subject's lower back to detect sweating. During exercise, the time of the start of the sweating, defined as the appearance of the first blue dots in the starch-iodine powder and the time of the start of whealing will be recorded.

Subjects will be rated after the PCE test on their number of wheals and their itch severity, resulting in a sum score for the Urticaria Activity Score post-provocation (UASprovo) ranging from 0 to 6 points.

a) Numbers of wheals (0 = 0; 1 to 20 wheals = 1; 20 to 50 wheals = 2; > 50 wheals = 3)

b) Itching (none = 0, mild = 1, moderate = 2, severe = 3)

11.3.2 Physician's Global Assessment of Disease Severity by VAS

The Physician's Global Assessment (PhGA) is an instrument used in clinical trials to rate the subject's current disease severity using a Visual Analogue Scale (VAS) ranging from 0 (absence) to 10 (worst possible severity).

The PhGA score will be assessed according to the schedule of trial procedures (Section 4). The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit.

The disease activity assessment score will be recorded in the eCRF.

11.3.3 Histamine Skin Prick Testing

The Histamine Skin Prick Testing (SPT) is widely accepted method used in allergy clinics to test for histamine sensitivity causing pruritus, skin flare and a skin wheal. A solution of the challenge agent will be applied using the skin prick method as described in The Global Allergy and Asthma European Network (GA^2LEN) Guidelines [27]. The skin prick method involves placing a drop of histamine solution onto the skin and using a lancet to gently pierce the superficial layer of the skin. The excess histamine is then wiped away.

- histamine
- negative control − saline

Pruritus during the SPT will be assessed by subjects every minute for 15 minutes total using a 100mm VAS scale with 0 indicating 'no itch' and 10 indicating 'worst itch imaginable'.

The absolute wheal/flare size will be measured.

A positive test is defined as a wheal and flare reaction (≥ 3mm in diameter relative to negative control). Study assessment will commence 15 - 20 mins after the skin has been pricked.

The Histamine SPT will be performed according to the schedule of trial procedures (Section 4).

The result (positive/negative), the wheal size and pruritus evaluation by subjects will be recorded in the eCRF.

11.3.4 Patient-reported outcomes

All patient-reported outcomes (PROs) in this trial will be provided to the subjects as paper versions.

11.3.4.1 Patient's Global Assessment of Severity by VAS

Patient's Global Assessment of Severity (PGA-S) is a single item designed to capture the subject's overall perception of their symptoms over the past week on a Visual Analogue Scale ranging from 0 (absence) to 10 [28]. The PGA-S will be completed at the trial site according to the schedule of trial procedures in Section 4.

11.3.4.2 Urticaria Control Test

Subjects will complete the UCT and mUCT questionnaire at visits according to the schedule of trial procedures (Section 4). The UCT is a disease-specific measure consisting of four questions that retrospectively assesses patients' burden of disease over the previous 4 weeks. For this study, in addition to having patients complete the traditional UCT, the recall period will be modified to assess the burden of disease over the past week (mUCT) to capture changes over a shorter recall period. Concepts covered include disease activity, QoL survey, disease control, and therapy. Each of the four questions are scored on a scale of 0 to 4 (see Panel 7). The UCT score is derived by adding up the scores from each of the four questions. A total score from 0 (no control) to 16 points (complete control) is derived, with a score of ≥ 12 indicating well-controlled disease. The UCT has high levels of validity and reliability, and accurately identifies patients with insufficiently controlled disease. Its minimal clinically important difference (MCID) is 3 points [29].

Panel 7: (Modified) Urticaria Control Test

1. How much have you suffered from the physical symptoms of the urticaria (itch, hives (welts) and/or swelling) in the last four weeks (in the last week)* very much (0) much (1) somewhat (2) a little (3) not at all (4)
2. How much was your quality of life affected by the urticaria in the last 4 weeks (in the last week)? very much (0) much (1) somewhat (2) a little (3) not at all (4)
3. How often was the treatment for your urticaria in the last 4 weeks (in the last week) not enough to control your urticaria symptoms? very often (0) often (1) sometimes (2) seldom (3) not at all (4)
4. Overall, how well have you had your urticaria under control in the last 4 weeks (in the last week) not at all (0) a little (1) somewhat (2) well (3) very well (4)

* wording for mUCT is given in brackets

11.3.4.3 Cholinergic Urticaria Activity Score 7

The Cholinergic Urticaria Activity Score 7 (CholUAS7) is a validated tool to assess disease symptoms in CholU subjects [30], consisting of overall 4 different items. Among all items of the CholUAS7, the hive severity score (HSS) and the itch severity score (ISS) will be summed over 7 days using once daily diary-based documentation. The weekly CholUAS7 for these 2 items is the sum of the daily HSS score and the daily ISS score for 7 consecutive days. The possible range of the weekly UAS7 score based on the HSS and the ISS is 0-42 with higher values indicating higher disease severity [9].

Hive count

The wheals (hive) severity score (HSS) defined by the number of hives, will be recorded by the subject once daily in their diary on a scale of 0 (none) to 3 (intense/severe) see Panel 8. A weekly score (HSS7) is derived by adding up the daily scores of the 7 days preceding the visit. The possible range of the weekly score is 0-21 with higher values indicating greater hives severity.

Panel 8: Hive severity score

Score	Wheals (Hives)
0	None
1	Mild (1-20 hives/24 hours)
2	Moderate (21 – 50 hives /24 hours)
3	Severe (>51 hives /24 hours)

Handling of missing data when calculating the HSS7:

If a subject has at least 5 available daily scores within the 7 days prior to the study visit, the weekly score is calculated as the sum of the available daily scores in that week, divided by the number of days with the available score, multiplied by 7. If there are less than 5 available daily scores within the prior 7 days, then the weekly score is missing for the week.

Itch severity score (ISS):

The severity if the itch will be recorded by the subject daily in their diary on a scale of 0 (none) to 3 (intense/severe) (see Panel 9). A weekly score (ISS7) is derived by adding up the daily scores of the 7 days preceding the visit.

Panel 9: Itch severity score

Score	Pruritus (Itch)
0	None
1	Mild (minimal awareness, easily tolerable)
2	Moderate (definite awareness, bothersome but tolerable)
3	Severe (difficult to tolerate)

Handling of missing data when calculating the ISS7:

If a subject has at least 5 available daily scores within the 7 days prior to the study visit, the weekly score is calculated as the sum of the available daily scores in that week, divided by the number of days with available score multiplied by 7. If there are less than 5 available daily scores within the prior 7 days, then the weekly score is missing for this week.

11.4 Safety assessments

11.4.1 Vital signs

Vital signs (resting blood pressure, pulse, and body temperature) must be assessed according to the schedule of trial procedures (Section 4) and prior to randomisation. Vital signs will be measured following at least 5 minutes of rest.

If an abnormal vital sign at screening and/or baseline is considered to be clinically significant by the investigator, it will be at the discretion of the investigator if the subject should be randomised into the trial. During the trial, if a subject presenting with a clinically significant abnormal vital sign, the investigator must take appropriate action, at their discretion.

In case of abnormal findings, the vital sign measurement can be repeated approximately 15 minutes later to verify the first measurement. Should the repeated measurement result in a normal value, the measurement must be repeated once more. If the third measurement verifies the second (normal) value, the first measurement should be considered false and the second measurement should be recorded in the eCRF. If the third measurement confirms the first measurement (abnormal), the second measurement will be considered false and the first measurement should be recorded in the eCRF.

Reporting in eCRF
It will be recorded in the eCRF if vital signs were measured; if not, a reason should be provided. Vital signs, arm used to measure blood pressure, the temperature measuring method (axillary, ear, oral, rectal, other), and the date and time vital signs were measured will be recorded in the eCRF. Clinically significant abnormal vital signs at the screening visit and baseline (as the subjects has not been administered treatment) will be documented as medical history in the eCRF. At subsequent visits, any clinically significant deterioration of a pre-existing condition as well as any new clinically significant sign, symptom, or illness occurring after randomisation will be reported as an AE in accordance with Section 0.

11.4.2 Physical examination

A physical examination of the subject including general appearance, regional lymph nodes, and dermatologic examination of the skin must be conducted according to the schedule of trial procedures (Section 4). Subjects with clinically significant findings on physical examination meeting any of the exclusion criteria (Section 8.3) must not be randomised.

Reporting in eCRF
It will be recorded in the eCRF if a physical examination was performed and, if applicable, the investigator's evaluation ('normal', 'abnormal, not clinically significant', 'abnormal, clinically significant'); if a physical examination was not performed, a reason should be given.

Clinically significant abnormal findings at the screening visit will be documented as medical history in the eCRF. At subsequent visits, any clinically significant deterioration of a pre-existing condition as well as any new clinically significant sign, symptom or illness occurring after randomisation will be reported as an AE in accordance with Section 13.3.

11.4.3 ECG

A 12-lead resting digital ECG will be recorded after the subject has been supine for at least 5 minutes at the visits indicated in the schedule of trial procedures (Section 4). ECGs must be measured before any blood samples scheduled at the same visit. At the screening visit 3 consecutive ECGs must be measured and the average QTcF derived (see exclusion criterion 6).

At baseline visits for each treatment period, V3 and V5 post dose ECGs must be measured 1 hour±15 min after IMP dosing at the site.

A pre-evaluation of the ECGs will be performed by the investigators to evaluate immediate subject safety. In case of a suspected abnormal ECG, the investigator must take appropriate action, as further detailed below. At a minimum, the date of ECG collection will be recorded in the source documents.

The ECG data will be transferred to a central ECG service company for central evaluation. A cardiologist at the ECG service company will analyse and interpret the ECG data. The ECG service company will provide ECG evaluation reports to the trial sites. The investigator must evaluate all abnormal ECG results ('clinically significant' or 'not clinically significant') and sign and date. The investigator is responsible for taking the final decision about the clinical significance of any abnormal ECG.

Subjects with a clinically significant abnormal ECG at screening must not be included in the trial (exclusion criterion 6). In addition, subjects meeting any of the exclusion criteria 7 and 8 must not be included in the trial. I.e. subjects with clinically significant ECG findings meeting any of the exclusion criteria (Section 8.3) must not be randomised.

If the subject presents with a severe QT-prolongation post-baseline (i.e. after the first use of the IMP), i.e. QTcF > 500 ms or a change in QTcF > 60 ms from baseline (pre-dose ECG), the ECG should be repeated. If the QTcF or change in QTcF from baseline (pre-dose ECG) are confirmed, the subject must permanently be discontinued from IMP and withdrawn from the trial.

If the subject presents with a moderate QT prolongation, i.e. 480 ms < QTcF ≤ 500 ms or 30 ms < change in QTcF from baseline (pre-dose ECG) ≤ 60 ms, the ECG should be repeated. If the QTcF or change in QTcF from baseline (pre-dose ECG) are confirmed, a subject at investigator's discretion may continue with the trial, but an additional ECG must be done at the safety follow-up in order to check if QTcF returned to normal values.

The collection and transmission of ECG data will be described in a separate ECG manual.

Reporting in eCRF
It must be recorded in the eCRF if an ECG was measured. If not, a reason must be provided. The investigator's assessment of ECG result ('normal', 'abnormal, not clinically significant', 'abnormal, clinically significant') must also be recorded in the eCRF.

Clinically significant abnormal ECG findings at the screening visit will be documented as medical history in the eCRF. At subsequent visits, any new clinically significant abnormal ECG finding, symptoms, or illnesses after randomisation will be reported as an AE in accordance with Section 13.3, as well in accordance with Section 13.6.1, as prolonged electrocardiogram QT corrected intervals will be regarded as an AE of special interest (AESI), considering QTcF > 450 ms as a clinically significant QT-prolongation.

11.4.4 Laboratory testing

11.4.4.1 Overview

Pregnancy tests in female subjects of child-bearing potential must be performed at visits according to the schedule of trial procedures (Section 4). At visit 1 (screening), a serum hCG test is to be made, on the other visits, urine hCG dip tests will be made. At visit 2 (start of treatment), the test must be made prior to randomisation. Pregnant women must not be randomised into the trial.
Blood and urine samples will be collected according to the schedule of trial procedures (Section 4).

SARS-CoV-2 test at Screening and if necessary, at further study visits will be performed according to current local regulations and requirements.

The evaluations shown in Panel 10 will be performed.

Panel 10: Clinical laboratory tests

Chemistry	Haematology
Sodium Potassium Magnesium Creatinine[1] Urea nitrogen Total and free calcium (albumin-corrected) Alkaline phosphatase Aspartate aminotransferase Alanine aminotransferase Gamma glutamyl transferase Bilirubin[2] Lactate dehydrogenase Cholesterol LDL cholesterol HDL cholesterol Triglycerides Glucose (non-fasting) Albumin Total Protein CRP	Erythrocytes Haematocrit Haemoglobin Erythrocyte mean corpuscular volume Erythrocyte mean corpuscular haemoglobin concentration Leukocytes Neutrophils Lymphocytes Monocytes Eosinophils Basophils Thrombocytes
	Serology[3]
	Hepatitis B virus surface antigen Hepatitis B virus surface antibody Hepatitis B virus core antibody Hepatitis C virus antibody HIV-1 antibody HIV-2 antibody
	Biomarker[4]
	IgE
	Serum pregnancy test[3,5]
	Choriogonadotropin beta (beta hCG)
	Local tests
	Urine pregnancy test[5]
	SARS-CoV-2 test[6]

1) Estimated glomerular filtration rate (eGFR) calculated with Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) creatinine equation
2) If bilirubin is above upper limit of normal, direct and indirect bilirubin will also be measured.
3) Measured at screening only.
4) At V2 to V5, only
5) Only women of childbearing potential.
6) In accordance with current local regulations and requirements; mandatory at screening only.

Abbreviations: HDL = high density lipoprotein; LDL = low density lipoprotein, CRP = C-reactive protein; HIV = human immunodeficiency virus, IgE = immunoglobulin E, SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2.

11.4.4.2 Investigator evaluation of laboratory samples

Central laboratory

Chemistry, haematology, serology, and serum pregnancy tests will be analysed by a central laboratory which will provide results to the trial sites. The investigator must evaluate all results outside the reference range ('clinically significant' or 'not clinically significant') and sign and date the evaluation. The signed and dated version will be filed with the investigator's trial documentation. Clinically significant abnormal tests must be repeated to confirm the abnormality.

If a screening laboratory result is abnormal and of clinical significance, it will be at the investigator's discretion to decide if the subject should be randomised into the trial. During the trial, if a subject presents with a clinically significant abnormal laboratory result, the investigator must take appropriate action, at their discretion (see also Section 10.2).

A laboratory manual will be provided to the trial sites specifying the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information specific to this trial.

Tests performed at the trial site

Women of childbearing potential will have a urine pregnancy test with a dipstick performed at the trial site at baseline prior to randomisation. A woman with a positive urine pregnancy test at Week 0 (baseline) must not be randomised in the trial. During the trial the test will be performed at trial visits as displayed in the schedule of trial procedures in Section 4. A woman with a positive urine pregnancy test during the trial must immediately and permanently discontinue IMP and be withdrawn from the trial. A positive urine pregnancy test must be verified with a serum pregnancy test.

Reporting in eCRF

The site staff will record in the eCRF if a blood sample was taken, if not, a reason should be provided. The date the sample was taken as well as the investigator's assessment of the results ('normal', 'abnormal, not clinically significant', 'abnormal, clinically significant') will be recorded in the eCRF.

It will be recorded in the eCRF if the subject is a woman of childbearing potential and if a urine pregnancy test was performed, if not, a reason should be provided. Also, the date and the outcome of the urine pregnancy test will be recorded in the eCRF ('positive', 'negative').

Clinically significant abnormal laboratory results at the screening visit will be documented as medical history in the eCRF. At subsequent visits, any clinically significant deterioration of a pre-existing condition will be reported as an AE. Any new clinically significant sign, symptom, or illness occurring after randomisation will be reported as an AE in accordance with Section 13.3.

11.4.5 Test for SARS-CoV-2 infection

A test for active SARS-CoV-2 infection (COVID-19) is required for all subjects at screening. Testing will be performed in accordance with institutional guidelines and national/local regulations.

At subsequent visits subjects will be monitored for SARS-CoV-2. If an active SARS-CoV-2 infection is suspected, the respective testing should be performed at the discretion of the investigator.

Results will only be recorded in subject's medical record.

Subjects with active and confirmed SARS-CoV-2 infection will be managed in accordance with institutional guidelines with regards to trial site visits.

11.5 Pharmacokinetic assessments

11.5.1 Blood sampling for analysis of drug

Blood samples for PK assessments will be collected at the visits as specified in the schedule of trial procedures (Section 4).

PK blood sampling should be performed at baseline of each treatment period after IMP intake at site and at V3 and V5 prior to and approximately CCI [redacted] after administration of the IMP on site.

Reporting in eCRF
It will be recorded in the eCRF if the PK sample was taken; if not, a reason will be provided. The date and time of the last IMP administration prior to the PK sample being taken must be recorded in the eCRF.

Collection, handling, and shipment instructions for PK blood samples are provided in a laboratory manual.

11.6 Pharmacodynamics assessments

Biomarkers will be analysed to evaluate pharmacodynamic markers of drug effects. Samples for assessment of biomarkers in blood samples and skin biopsies will be collected at the time points specified in the schedule of trial procedures (Section 4). Taking of skin biopsies is optional.

11.6.1 Blood biomarkers

Serum samples for biomarker analyses (proteomics and IgE) will be taken according to the schedule of trial procedures (Section 4). Serum sampling for biomarker analysis at baseline visits (i.e. visit 2 and visit 4/4a) should be taken prior to the intake of the IMP and sampling at the end of treatment visits (i.e. visit 3 and visit 5) for each of the treatment periods should be done after the IMP intake. It will be recorded in the eCRF if the sample was taken; if not, a comment should be provided.

Collection, handling, and shipment instructions for serum biomarker samples are provided in a separate laboratory manual.

Results will be included in the CTR.

11.6.2 Skin biopsies

Subjects will be asked to participate in an exploratory component involving skin biopsies. Participation in this component of the trial requires that the subject provides additional informed consent.

3 mm skin punch biopsies for histologic analysis and transcriptomics will be taken at the time-points specified in the schedule of trial procedures (Section 4). At visit 2 (day 1), two non-lesional biopsies (from an area, that usually develops wheal and flare upon provocation) will be taken prior to the provocation test and two lesional biopsies will be taken, after the provocation test. At visit 3 (day 8), subjects will have two biopsies performed on non-lesional skin prior to the provocation test.

It will be recorded in the eCRF if skin biopsies were taken from the lesional and non-lesional area as described above; if a skin biopsy was not taken, a reason will be provided.

A check of skin biopsy wound healing including removal of suture, if applicable, will be performed at the next trial visit (at visit 3 or visit 4, respectively).

Collection, handling, and shipment instructions for skin biopsy samples are provided in a separate laboratory manual.

Results will be included in the CTR.

11.7 Other assessments

11.7.1 Patient-reported outcomes

Each subject must make individual assessments relating to their perception of their disease and quality of life. These will be performed prior to the investigator performing his/her efficacy assessments. All PROs will be provided to the subjects in paper versions and data will be transferred into the eCRF by site personnel.

11.7.1.1 Diary

At screening the subjects will receive a paper diary to document the CholUAS7 (see Section 11.3.4.3) and the use of medications taken to treat their disease symptoms as well as of other medications (except usual ongoing medication), if any. The subjects need to complete the diary each day throughout the whole trial duration.

During the treatment periods the subject should also document the intake of IMP specifying date and time. Compliance with the diary completion will be reviewed by the trial site staff at each visit. The diary will be collected to the site as outlined in the schedule of trial procedures (Section 4).

11.7.1.2 Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI) is a validated questionnaire with content specific to those with dermatology conditions [31]. It consists of 10 items addressing the subject's perception of the impact of their skin disease on different aspects of their quality of life over the last week such as dermatology-related symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the treatment. Each item is scored on a 4-point Likert scale (0 = 'not at all⁄not relevant'; 1 = 'a little'; 2 = 'a lot'; 3 = 'very much'). The total score is the sum of the 10 items (0 to 30); a high score is indicative of a poor quality of life. The DLQI will be completed at the trial site according to the schedule of trial procedures in Section 4.

11.7.1.3 Cholinergic Urticaria Quality of Life Questionnaire

The cholinergic urticaria quality of life questionnaire (CholU-QoL) is validated questionnaire with content specific to those with conditions of cholinergic urticaria [32]. It consists of 28-items, addressing 5 different aspects over the last 7 days (symptoms, functional life, social interaction, therapy and emotions). Each item is score with 5-point Likert scale (LS) with the answer options “not at all”; “somewhat”; “moderately”; “much”; “very much” as well as “never,” “seldom,” “occasionally,” “often” and “very often”.

The CholU-QoL will be completed at the trial site according to the schedule of trial procedures in Section 4.

11.7.2 Photography

Subjects who consented in skin biopsy will have a mandatory photography component of the biopsy site. The digital photography assessments will serve as documentation of biopsy location to check for possible irregularities in case of unexpected results. No further evaluations or publications are planned. Consent to this photography component will be requested in the additional informed consent for the biopsies.

Digital colour photographs will be taken of the selected skin area for biopsies before the biopsy according to the schedule of trial procedures (Section 4). It will be recorded in the eCRF if at least one photo was taken; if not, a comment should be provided.

The trial sites will use their own equipment to take the photographs and photographs will be stored at trial sites according to local practice and local regulations.

Visit date and time of photography should be indicated on the images. Beside this information the photographs will have no other subject identifier than the subject ID.

Images will be transmitted electronically to LEO Pharma using a secure file transfer protocol and will solely be used to evaluate the biopsy sites in case of suspected irregularities. Images will be stored for no longer than 12 months after completion of the CTR.

11.8 End of trial

End of treatment form

An end of treatment form will be completed in the eCRF for all subjects when they have had their last administration of IMP in any treatment period. This form will also be completed for subjects who permanently discontinue IMP and subjects who withdraw from trial (see Section 10.3 for early termination assessments).

The date and time of last administration of IMP will be recorded on the end of treatment form. It will also be recorded if the subject completed the treatment. If not, the primary reason for permanent discontinuation of IMP must be recorded (see Section 10.2.1).

End of trial form

An end of trial form must be completed in the eCRF for all screened subjects. The following data will be collected:

- Screening failure.
- Did the subject complete the trial.
- Which was the last visit (including phone call) the subject attended in this trial.
- Date of last contact.
- Primary reason for withdrawing from the trial (death, pregnancy, adverse event, lack of efficacy, screening failure, withdrawal by subject, lost to follow-up, or other [if other, a specification should be provided]).
- If the subject attended the primary endpoint visit (visit 5). If not, the primary reason for not attending the visit (death, pregnancy, adverse event, lack of efficacy, withdrawal by subject, lost to follow-up, or other [if other, a specification should be provided]).
- If the subject attended the safety follow-up visit (visit 6). If not, the primary reason for not attending the visit (death, pregnancy, adverse event, lack of efficacy, withdrawal by subject, lost to follow-up, or other [if other, a specification should be provided]).

The end of trial form will be completed when the subject turned out to be a screening failure or has had their last visit (that is the safety follow-up visit 6, or early termination visit).

11.9 Estimate of total blood volume collected

Blood samples will be drawn for haematology, biochemistry, serology, PK and PD. The total volume of blood to be drawn is approximately 100 mL. If additional blood samples are required, the amount of blood drawn may be more than this stated value; however, the total volume of blood drawn will be much less than that taken during a blood donation (approximately 500 mL).

11.10 Storage of biological samples

Laboratory samples (chemistry/haematology/serology) will not be stored for more than a few days after sampling and analysis.

Primary samples for PK will be discarded by the bioanalytical lab upon finalisation of the CTR whereas backup samples stored at the Central Lab will be retained for as long as the quality of the material permits evaluation but for no longer than 12 months after completion of the CTR. Any backup samples that have been sent to the Bioanalytical Lab will also be discarded upon finalisation of the CTR.

Biomarker samples (skin biopsies and PD blood samples) will be retained for as long as the quality of the material permits evaluation but for no longer than 12 months after completion of the CTR unless the subject has given additional consent allowing storage in a biobank for future research.

If the subject consents to this, LEO Pharma will store these biomarker samples and/or the material isolated from these biomarker samples in a biobank established by LEO Pharma and hosted by Brooks Life Sciences. The residual biological samples will be used for future research conducted by LEO Pharma. The samples will be transferred from the relevant laboratory to the biobank. The samples will be labelled with the trial ID, subject ID, and sample date to protect the privacy of the subjects and to allow continued blinding for future analyses. The samples will be stored in the biobank for as long as the quality of the material permits evaluation and will then be destroyed.

12Scientific rationale for trial design and appropriateness of assessments

12.1 Scientific rationale for trial design

EXP-2177 is a randomised, double-blind, placebo-controlled, multi-centre, 7-day cross-over trial. The cross-over trial design is optimal to ensure a clear and unbiased evaluation of the efficacy and safety of the drug effects since each subject serves as his/her own placebo control. This 7-day cross-over trial design is possible due to the short IMP half-life, expected rapid onset of action, and inducible nature of the signs/symptoms of CholU with a provocation test (UASprovo [9, 31]). The treatment periods consist of 7-day treatment each with LEO 152020 or placebo. The placebo treatment period will serve as a reference and has been added to establish efficacy and safety of LEO 152020. The use of placebo is considered to be appropriate because of the short treatment period. Randomisation to the sequential order of treatment periods will minimize allocation bias and baseline confounding, as well as permit the evaluation of any possible carry-over effect(s) from treatment with LEO 152020. Double-blinding will minimize ascertainment bias.

IMP will be supplied as CCI tablets with C mg free based per tablet. Dose is CCI for 7 days. The dose of CCI mg daily is chosen based on the predicted efficacious dose from an ex vivo pharmacodynamic assay (e.g. eosinophil shape change assay). Divided dosing ensures high exposure around the clock. The medication will be administered with an interval of at least 9 hours between dosing and as specified in Section 9.2. Steady state concentration is expected to be reached in 2-3 days (half-life 6-7 hours), therefore a short treatment period of 7 days is possible.

The trial population is adult patients with CholU that are poorly controlled based on the UCT [33]. Subjects will have a recent history (within 6 months) with documented inadequate response to standard dose (as to marketing authorization) H1 antihistamines, which is the current standard of care for CholU. This trial population represents the patients with highest remaining unmet clinical need and can be applied to the general population.

Due to the potential important risk of QT prolongation, exclusion criteria are in place to exclude subjects at risk (see Section 8.3 for the exclusion criteria and Section 5.5 for more information about mitigation of the risk of QT prolongation). The other eligibility criteria have been chosen to ensure inclusion of the targeted patient population and safety of the subjects and to minimize factors which could interfere with the efficacy and safety assessments (Sections 8.2 and 8.3).

12.2 Appropriateness of assessments

Patient-related outcomes are important to be looked at in the treatment for urticaria including CholU. A number of questionnaires and scores have been developed and are widely used to assess treatment efficacy. For evaluation of the disease severity and treatment effects the UAS [34] is used, a generally recognised instrument for the assessment of disease severity of CholU. Due to the inducible character of the disease the signs/symptoms of CholU will be evaluated after a provocation test (UASprovo) [9, 26].

Further assessments as UCT [33], CholUAS7 and CholU-QoL are also widely used and validated assessments for determination of disease severity and impact on quality of life and changes thereof.

To gain more information about the mechanism /mode of action of the potential treatment benefit pharmacodynamic assessments in terms of evaluation of biomarkers in blood and skin will be assessed.

13 Adverse events

13.1 Definition and classification of adverse events

Adverse events (AEs) and serious adverse events (SAEs) are defined in Appendix 1.

Classification of AEs in terms of severity, causality and outcome is defined in Appendix 2.

13.2 Collection of adverse event reports

AE data must be collected from time of first trial-related activity after the subject has signed the informed consent form (ICF) until subject's completion of the clinical trial (all trial periods including the safety follow-up visit (visit 6) see Section 7.3).

AEs must be assessed by medically qualified personnel.

At all visits, the subject will be asked a non-leading question by the investigator about AEs, e.g.: "How have you felt since I saw you last?" No specific symptoms should be asked for. It is important that the investigator also observes the subject for any changes not reported by the subject and records these changes.

Principles for data recording in the eCRF are described in Sections 11.4.1 to 11.4.5.

13.3 Reporting of adverse events

AEs reported by the subject or observed by the investigator must be recorded on the AE form of the eCRF and should be described in the following manner:

The *AE term* must be in precise English medical terminology (that is, not necessarily the exact words used by the subject). Whenever possible, a specific diagnosis should be stated (for example 'allergic contact dermatitis').

The *duration* of the AE must be reported by the start date and stop date of the event, unless the event is ongoing. If the event is ongoing, it will be marked as ongoing. In addition, it will be recorded if the AE started prior to first administration of IMP in treatment period A or treatment period B, respectively.

AEs must be classified in terms of severity, causality, and outcome according to the definitions in Appendix 2.

Action taken with IMP: any action taken with IMP as a consequence of the AE must be recorded (dose not changed, drug interrupted, drug withdrawn, not applicable, unknown).

Other action taken: any other action taken as a result of the AE must be recorded (none, concomitant medication, concurrent procedure).

Withdrawn from trial due to this AE: it must be recorded whether the AE led to withdrawal from the trial.

13.4 Reporting of serious adverse events

The criteria that define an AE as serious (that is, an SAE) are defined in Appendix 1. SAE criteria are also listed on the SAE form.

13.4.1 Investigator reporting responsibilities

Any SAE must be reported to LEO Pharma on the (paper) SAE form immediately, without undue delay but not later than within 24 hours of first knowledge. This report should contain amongst others an assessment of available information on seriousness, severity, causal relationship to the IMP(s) or trial procedure, the action taken, the outcome to date, and a narrative description of the course of the event. For more details regarding reporting of any SAE, please see the guidance text on the SAE form.

By signing and dating the SAE form, the investigator acknowledges that he/she is aware of the SAE and has assessed the causal relationship of the IMP(s) and any of the other medications to the SAE.

The actual reporter, if not the investigator, should also sign and date the SAE report.

The completed SAE form must be faxed or scanned and e-mailed to Global Safety at LEO Pharma using the e-mail address or fax number below:

Global Safety at LEO Pharma

E-mail address: drug.safety@leo-pharma.com

Fax number: +45 69102468

If relevant, the investigator will enclose other information with the SAE form, such as anonymised reports of diagnostic procedures, hospital records, autopsy reports, etc.

Additionally, Global Safety at LEO Pharma may request further information in order to fully assess the SAE. The investigator must forward such information to LEO Pharma upon request by fax or e-mail (see contact details above).

The investigator must notify the local IEC(s) of SAEs, as required by current applicable legislation for the concerned country.

SAEs occurring after the completion of the clinical trial should not routinely sought or collected. However, such events should be reported to Global Safety at LEO Pharma (see contact details above) if the investigator becomes aware of them.

13.4.2 LEO reporting responsibilities

Global Safety at LEO Pharma is responsible for assessing whether an SAE is expected. The relevant reference safety information document for this clinical trial is the IB, Section 7.2 ed. 3.0 [8] and subsequent updates.

Global Safety at LEO Pharma will notify the regulatory authorities and concerned investigators of SAEs according to the current applicable legislation for the concerned country.

The IEC(s) will be notified of SAEs according to the current applicable legislation for the concerned country.

For all non-US countries, the following reporting requirements apply: all SAEs which are assessed as causally related to the IMP by either the investigator or LEO Pharma [35], and which are unexpected (suspected, unexpected serious adverse reactions [SUSARs]), are subject to expedited reporting to regulatory authorities, IEC(s)) according to the current applicable legislation in the concerned country. Investigators will be notified of the evolving safety profile of the IMP on an ongoing basis.

13.5 Other events that require expedited reporting

13.5.1 Pregnancy

Any pregnancy occurring after first exposure to IMP and until the subject has completed the trial must be reported to LEO Pharma within 24 hours of first knowledge using the (paper) pregnancy form (part I). All pregnancies must be followed up until delivery or termination, and outcome must be reported on the (paper) pregnancy form (part II) within 24 hours of first knowledge.

The completed pregnancy forms must be faxed or scanned and e-mailed to Global Safety at LEO Pharma. Contact details are given in Section 13.4.1.

Pregnant subjects must immediately discontinue IMP permanently (Sections 10.2.1 and 10.3).

In the eCRF pregnancy should be provided as reason for withdrawal (see Section 10.2.1).

13.5.2 Adverse events of special interest

AEs considered AESIs in this trial are described in more detail in Section 13.6.1. If an AESI qualifies as an SAE, expedited reporting will be required (Section 13.4).

13.6 Reporting of other events

13.6.1 Adverse events of special interest

The events listed in Panel 11 are considered AESIs in this trial and will require additional data to be recorded in the eCRF. LEO Pharma may request that the investigator forwards additional test results, as appropriate. An AESI may be serious or non-serious. Serious AESIs require expedited reporting via the SAE form as described in Section 13.4.

Panel 11: Adverse events of special interest

Adverse event of special interest	Additional data to be recorded	Data collection method
Electrocardiogram QT corrected interval prolonged	• ECG (measured at relevant timepoints according to the schedule of trial procedures [Section 4]). • Severity of the QT/QTcF prolongation (mild, moderate, severe, see severity criteria in Panel 12). • Symptoms believed to be related to the QT/QTcF prolongation and duration of the symptoms.	eCRF For serious cases, the safety database as per procedure

Abbreviations: ECG = electrocardiogram; eCRF = electronic case report form; QT = QT interval; QTcF = QT interval corrected by Fridericia's formula.

AESIs of electrocardiogram QT corrected interval prolonged

If at any ECG measurement a subject presenting with QTc >450 ms, this must be reported as an AE if it occurs after intake of IMP at day 1. Severity of the AE must be reported in the eCRF (see Panel 12 for guidance). Clinically significant abnormal findings at the screening visit will be documented as medical history in the eCRF.

Panel 12: Severity specifications for adverse event of electrocardiogram QT corrected interval prolonged

Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)
450 ms< average QTc <480 ms	481 ms< average QTc <500 ms or 30 ms < change in QTc from baseline (pre-dose ECG) to measurement ≤ 60 ms	Average QTc ≥501 ms or Change in QTc from baseline (pre-dose ECG) to measurement >60 ms

Modified from (Common Terminology Criteria for Adverse Events [CTCAE] Version 5.0 [36])

13.6.2 Medication error

Medication error refers to any unintentional error in the dispensing or administration of an IMP while in the control of the investigator or subject. Medication errors include administration of wrong medication, wrong dose accidental overdose and underdose), wrong dosing schedule (CCI [redacted]), wrong route, and administration of expired IMP.

Reporting in eCRF

The medication error category must be documented on the AE form in the eCRF. Only accidental overdose or underdose and wrong dosing schedule where a clinical consequence occurred or could have occurred based on the investigator's judgement should be recorded in the eCRF. In addition, any clinical consequence of the medication error must be recorded as a separate AE on the AE form. If the AE originating from the medication error qualifies as an SAE, expedited reporting will be required (Section 13.4).

13.6.3 Misuse or Abuse

The terms misuse and abuse are similar in terms that they both represent the intentional use of a drug in a way other than intended.

Misuse refers to situations where the IMP is intentionally and inappropriately used for therapeutic purposes not in accordance with the protocol.

Abuse refers to situations where the IMP is intentionally used for what could be considered desirable non-therapeutic effects (e.g. sedative, stimulant, euphoric effects).

Misuse and abuse must be recorded on the AE form in the eCRF. In addition, any clinical consequence of misuse or abuse must be recorded as a separate AE on the AE form. If the AE

originating from the misuse or abuse qualifies as an SAE, expedited reporting will be required (Section 13.4).

13.6.4 Aggravation of condition

Any clinically significant aggravation/exacerbation/worsening of any medical condition(s) (including the trial disease), compared to screening, must be reported as an (S)AE in accordance with Sections 13.3 and 13.4.

13.7 Follow-up for final outcome of adverse events

During the trial, the investigator should follow up for final outcome on all AEs (including SAEs). Once a subject leaves the clinical trial, the investigator should follow up on the outcome of all non-serious AEs classified as possibly or probably related to the IMP until the safety follow up visit (visit 6) or until the final outcome is determined, whichever comes first. Non-serious AEs classified as not related to the IMP do not need to be followed up for the final outcome.

All SAEs must be followed up until a final outcome has been established, that is, the follow-up may continue beyond the end of the clinical trial. For SAEs which have stabilised and from which the subject cannot be expected to recover during the trial or the safety follow-up periods, e.g. chronic or stabilised conditions, the final outcome at the investigator's discretion should be reported as 'recovering/resolving' or 'not recovered/not resolved'. In addition, a statement detailing why the subject cannot be expected to recover during the trial, e.g. that the SAE has stabilised or is chronic, should be added to the narrative description of the SAE on the SAE form.

13.8 Handling of an urgent safety measure

An urgent safety measure is a measure taken to implement an action/protocol deviation under an emergency. This is defined as *"...the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard.*" [37].

If the investigator becomes aware of information that requires an immediate change in a clinical trial procedure or a temporary halt of the clinical trial to protect clinical trial subjects from any immediate hazard to their health and safety, the investigator can do so without prior approval from LEO Pharma, regulatory authorities, or IRBs/IECs.

The investigator must immediately inform LEO Pharma – by contacting the clinical project manager or medical expert – of this change in a clinical trial procedure or of the temporary halt; the investigator will provide full details of the information and the decision-making process leading to the implementation of the urgent safety measure.

LEO Pharma must act immediately upon receipt of the urgent safety measure notification in accordance with internal procedures and local legislation.

14 Statistical methods

14.1 Sample size

The sample size is based on the primary endpoint (change from baseline in UASprovo). A sample size of 28 randomised subjects with an assumed attrition rate of no more than 10%, i.e. less than 3 subjects to be excluded from analysis, will provide at least 25 subjects for analysis.

This is based on the following assumptions on distributional characteristics [9]:

- Baseline mean +/- SD = 4.7 +/- 1.1
- Placebo change from baseline 0.6 (12.8%)
- Active change from baseline 1.2 (25.5%)

Furthermore, the standard deviation is assumed to be reduced by 33% due to the intra-individual comparison implicit in the cross-over design. This follows from the removal of variation between subjects from the total variation of the endpoint, such that the standard deviation is assumed to be reduced from 1.1 to 0.73.

With a SD of 0.73 and alpha of 0.05, this will then provide at least 80% power for the hypothesis of a statistically significant difference between treatments, measured by UAS provocation test.

14.2 Trial analysis sets

All screened subjects will be accounted for in the CTR.

All subjects randomised will be included in the full analysis set and will be analysed for efficacy. Exclusions from the full analysis set (FAS) can be considered in special cases as described in ICH E9, Section 5.2.1, Full Analysis Set. If it is decided to exclude a randomised subject from the full analysis set, a justification addressing ICH E9 will be given.

A per protocol analysis set (PPS) will be defined by excluding subjects from the full analysis set who fulfil any of the following criteria:

- Receive treatment with at most one IMP.
- Provide no efficacy data following start of treatment.

- Are known to have taken the wrong IMP throughout at least one treatment period of the trial.
- Do not fulfil the disease defining inclusion criteria (that is, inclusion criteria 2, 3, and 6).

Further exclusion of subjects or subject data will be decided upon after a blind review of the data; this blinded review will include a review of all the remaining in- and exclusion criteria, concomitant medication that may affect trial disease, compliance/adherence issues, and violations of visit windows. Further exclusion of subjects or subject data may be considered based on input from the pharmacologist or in regard of the biomarker analysis.

A safety analysis set (SAF) will be defined as all subjects who received IMP.

A PK analysis set will be defined as all subjects who received IMP and provided samples for analysing plasma drug concentrations.

The decisions regarding inclusion/exclusion of subjects or subject data from the trial analysis sets will be documented in the minutes of the blind data review meeting, i.e. the document with analysis set definition before breaking the randomisation code and reported in the clinical trial report.

14.3 Statistical analysis

An observed-cases approach will be used for tabulations of data by visit (that is, involving only those subjects who attended each specific visit).

Parameters assessed during treatment periods will be summarised descriptively at baseline and at the end of the treatment period by treatment including change from baseline, where baseline is defined by treatment start within period. Unless otherwise specified descriptive statistics will additionally be presented for all measurements by treatment at each visit.

Categorical data will be summarised using the number and percentage of subjects in each category and treatment at each visit. Continuous data will be summarised using the mean, median, standard deviation (SD), minimum and maximum values.

A statistical analysis plan (SAP) will be written in addition to the protocol, including a more technical and detailed elaboration of the statistical analyses.

14.3.1 Disposition of subjects

The number of randomised subjects in each analysis set and the number of subjects who complete the trial will be given. The reasons for permanent discontinuation of IMP or withdrawal from trial will be presented for all randomised subjects by last visit attended and by treatment sequence.

14.3.2 Demographics and other baseline characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for all randomised subjects by treatment. Other baseline characteristics cover the subject's height and weight, the medical history, concomitant medication, and serology parameters. In addition, the investigator assessments UASprovo, histamins SPT, and PGA as well as the patient reported outcomes (CholUAS7, UCT, DLQI, CholU-QoL and the subject global assessment of severity will be summarised by treatment at treatment start within period. Presentations of age, sex, ethnicity, race will also be given by site.

14.3.3 Exposure and treatment compliance

The number of subjects exposed, the duration of exposure and the number of used tablets (administrations) will be tabulated. In addition, the number of subjects who complied with the IMP dosing schedule and instructions (yes, no) as well as the primary reason for non-compliance as provided in the eCRF will be given by period and treatment.

The duration of exposure to treatment in a specific visit interval will be calculated as the number of days from date of first administration of IMP in that period to the date of last administration of IMP in that period, both days included.

Exposure to treatment will be presented for the safety analysis set as days of exposure per treatment. Treatment compliance will be presented for the safety analysis set per treatment as the percentages of missed administrations.

14.3.4 Testing strategy

The primary efficacy endpoint will be compared between treatments by means of a linear mixed model. The analyses of all other efficacy endpoints are considered exploratory in this phase 2a trial. In addition, no interim analysis is planned. Therefore, there will be no adjustment for multiplicity and no further testing strategy necessary controlling the overall type I error rate.

14.3.5 Analysis of primary efficacy endpoint

The primary endpoint, change from baseline (V2 in treatment period A and V4 or V4a, respectively in treatment period B) in post-provocation Urticaria Activity Score (UASprovo) to the end of the treatment period, will be compared between treatments with the null hypothesis that they are equal against the alternative that they are different. The analysis will be performed both for the full analysis set (primary) and for the per protocol set (supportive) with imputing missing values at the end of treatment period (baseline value at the beginning of the period carried forward).

The primary efficacy endpoint will be analysed using a linear mixed model, containing treatment, period and carryover effects, the factor site and additionally the value of UASprovo at baseline as a covariate. Formally, if Y_{ijkl} denotes the change from baseline in UASprovo for subject i, treatment j and period k, then the following model equation will be used:

$$Y_{ijkl} = \mu + t_j + p_k + tp_{ik} + b_{ik} + s_l + \gamma_i + \varepsilon_{ijk},$$

where μ is the overall mean, t_j is the j-th treatment (j=1,2), p_k is the k-th period (k=1,2), s_l is the l-th site, tp_{ik} is the treatment-period interaction, which represents the carry-over effect, b_{ik} is the baseline value of UASprovo at V2 (k=1) and V4 or V4a (k=2), respectively, γ_i (i=1,…,n) is the random subjects effect, and ε_{ijkl} is the residual random error.

It will be assumed that the random subject effects as well as the residual errors are normally distributed. Both terms will be assumed to be independent. Within each subject, the residual random errors will be allowed to be correlated, assuming a compound symmetry covariance structure.

In a first step, the hypothesis H_0: tp = 0 vs. H_1: tp ≠ 0 will be tested. If H_0 cannot be rejected, it will be assumed that no carry-over effect is present. Analysis will then proceed as follows:

The interaction term will be deleted from the model, and the model without the interaction term will be fitted to the data. To test the effect of treatment on the primary efficacy endpoint, the hypothesis H_0: t = 0 vs H_1: t ≠ 0 will be tested, and a two-sided 95% confidence interval will be provided for the difference between treatments in addition to the test probability. In addition, least square means for each treatment will be provided.

In case a carry-over effect is present, the model will remain unchanged, and least square means are calculated, but no testing will be performed.

UASprovo will be summarised as mean, SD, median, minimum and maximum values at baseline as well as at the end of treatment period by treatment. Changes from baseline will also be included. For the visit at the end of the treatment period (visit 3, visit 5 respectively) both observed data and completed data (with missing data imputed using baseline value carried forward) will be presented. Means will be plotted by sequence and period. In addition, subject profiles will be displayed by treatment, separately for each sequence.

14.3.6 Analysis of secondary efficacy endpoints

The analyses of all secondary efficacy endpoints are considered exploratory in this phase 2a trial and will be analysed for the full analysis set. Only subjects with available data at baseline as well as at the end of the treatment period for at least one period will be included in the analysis.

There will be no adjustment for multiplicity.

Panel 13: Overview of statistical analyses for secondary efficacy endpoints

Endpoint	Hypothesis	Methods of analysis
Change from baseline in CholUAS7 at the end of the treatment period	Difference between treatments measured by change in CholUAS7 is different from zero	Linear mixed model
Change from baseline in UCT at the end of the treatment period	Difference between treatments measured by change in UCT is different from zero	Linear mixed model
Change from baseline in PhGA of disease severity at the end of the treatment period by VAS	Difference between treatments measured by change in physician's global assessment of disease severity is different from zero	Linear mixed model
Change from baseline in PGA-S at the end of the treatment period by VAS	Difference between treatments measured by change in patient's global assessment of severity is different from zero	Linear mixed model
Change from baseline in time to onset of provocation-induced whealing at the end of the treatment period	Difference between treatments measured by change in time to onset is different from zero	Linear mixed model
Change from baseline in time to onset of provocation-induced sweating at the end of the treatment period	Difference between treatments measured by change in time to onset of provocation induced sweating is different from zero	Linear mixed model
Change from baseline of histamine SPT wheal/flare size.	Difference between treatments measured by change in proportion of responders is different from zero	Linear mixed model

Endpoint	Hypothesis	Methods of analysis
Change from baseline of pruritus assessed at histamine SPT.	Difference between treatments measured by change in pruritus is different from zero	Linear mixed model
Change from baseline in DLQI at the end of the treatment period	Difference between treatments measured change from baseline in DLQI is different from zero	Linear mixed model
Change from baseline in CholU-QoL at the end of the treatment period	Difference between treatments measured by change in CholU-QoL is different from zero	Linear mixed model

See List of abbreviations for explanation of abbreviations used in the panel

The exploratory endpoints change from baseline at the end of treatment period of the parameters (CholUAS7, UCT, Physician's Global Assessment by VAS, Patient's Global Assessment by VAS, time to onset of provocation induced sweating and whealing, respectively, histamine SPT wheal/flare size and pruritus assessed at histamine SPT, as well as (total) DLQI, CholU-QoL) will be analysed using linear mixed models, with the same assumptions and the same model equation as finally applied for the primary endpoint, containing treatment effects, period effects and the baseline value of the respective endpoint at V2 and V4 or V4a, respectively. A carryover effect will be only included if it is contained in the final model for the analysis of the primary endpoint.

Estimated difference between treatments, two-sided 95% confidence intervals and least square means will be presented in addition to the test probability.

Each parameter (CholUAS7, UCT; Physician's Global Assessment by VAS, Patient's Global assessment by VAS, time to onset of provocation induced sweating and whealing, respectively, as well as (total) DLQI, CholU-QoL) will be summarised as mean, SD, median, minimum and maximum values by treatment including changes from baseline of the corresponding treatment period.

In addition, absolute wheal/flare size and the extent of pruritus during SPT, assessed by the subject, will be summarised as mean, SD, median, minimum and maximum values by treatment. Derivation of extent of pruritus measured every minute for 15 minutes in total during histamine SPT will be further specified in the SAP.

14.3.7 Analysis of patient-reported outcomes

Descriptive statistics (mean, SD, median, minimum and maximum values) will be presented at each visit by treatment for:

- UCT questions covering disease activity, QoL survey, disease control, therapy
- CholUAS-7 subscores wheals (hive) severity score (HSS) and itch severity score (ISS)
- DLQI subdomains concerning dermatology-related symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the treatment
- CholU-QoL subdomains addressing the aspects symptoms, functional life, social interaction, therapy and emotions.

Parameters will be analysed for the full analysis set.

14.3.8 Analysis of pharmacodynamics and pharmacogenomics

Descriptive statistics will be presented for the change from baseline in expression of disease biomarkers in blood and skin to the end of the treatment period by treatment. Disease biomarkers are specified in Section 11.6.

Disease biomarkers will be analysed for the full analysis set but will not be evaluated for all subjects. Further details will be specified in the statistical analysis plan.

14.3.9 Analysis of safety

The analysis of safety will be based on the safety analysis set.

14.3.9.1 Adverse events

AEs will be coded during the course of the trial according to Medical Dictionary for Regulatory Activities (MedDRA). AEs will be presented by preferred term and primary system organ class (SOC).

Treatment-emergent AEs will be summarised; however, all AEs recorded during the course of the trial will be included in subject data listings. An event will be considered treatment-emergent if started after the first use of IMP in each treatment period or if started before the first use of IMP and worsened in severity after first dose of IMP in each treatment period. The tabulations described in the following will only include the treatment-emergent events summarised according to the onset of AE. In each of the tabulations, AEs are defined by MedDRA preferred terms within primary SOC.

An overall summary of the number of events and the number (percentage) of subjects with any treatment-emergent AEs, deaths, SAEs, premature discontinuations from the trial due to AEs, treatment-related AEs, and severe AEs will be presented.

The number of AEs and number of subjects with AEs will be tabulated by SOC and PT for each treatment. The percentage of subjects with AEs will be compared between treatments by Fisher's exact test.

Related AEs are defined as AEs for which the investigator has not described the causal relationship to IMP as 'not related'. The number of related AEs and the number of subjects with each type of related AE will be tabulated. The percentage of subjects with related AEs will be compared between treatments by Fisher's exact test.

AEs which start during wash out phase or during follow-up phase within 3 days after last administration of IMP will be allocated as treatment-emergent AEs to the treatment applied in the prior period. In addition, AEs will be listed that do not have an outcome before the beginning of the second treatment period.

AESIs, defined as prolonged Electrocardiogram QT corrected interval will be listed by treatment. AESIs will in addition be presented by severity categories, as severity of AESIs will be categorized based on CTCAE (Version 5.0) [36].

SAEs and AESIs will be evaluated separately. Narrative will be provided for SAEs and serious AESIs.

AEs leading to withdrawal from trial and/or permanent discontinuation of IMP will be tabulated and listed. The detailed listing will provide an overview of the individual cases and include the age and sex of the subject, treatment received at the time of AE onset, the AE preferred and reported terms, causality and severity of the AE, the action taken with the IMP, AE outcome, start and stop date of AE, duration of AE, and number of days since first and last IMP administration. No narratives will be given.

14.3.9.2 Vital signs

Vital signs (resting blood pressure, pulse, and body temperature) will be summarised as mean, standard deviation (SD), median, minimum, and maximum values at each scheduled visit during screening, treatment periods and at the end of follow-up by treatment.

Similar tables will also be provided for each of the vital signs at baseline and at the end of the treatment period (visit 2 and visit 3, visit 4 or visit 4a, if applicable and visit 5, respectively)

by treatment. In addition, change from baseline to the end of treatment period will be included in the tabular display.

14.3.9.3 Physical examination

Physical examination findings will be assessed by the investigator as ‘normal’, ‘abnormal, not clinically significant’ or ‘abnormal, clinically significant’. A shift table will be produced showing for each treatment period the categories at baseline against those at the end of the treatment period by treatment. Subjects with abnormal and clinically significant findings at physical examination will be listed.

14.3.9.4 ECG

All of the ECG parameters (QTc, QTcF, QTcB) which are centrally evaluated will be summarised as mean, standard deviation (SD), median, minimum, and maximum values at each scheduled visit during screening and the treatment periods by treatment.

Similar tables will also be provided for each of the ECG parameter at baseline after first IMP administration and at the end of the treatment period before and after the last IMP administration by treatment. Change from screening will be included in the tabular display.

In addition, the change prior to post administration of IMP at the end of each treatment period will be summarised by treatment.

ECGs results will be assessed by the investigator as ‘normal’, ‘abnormal, not clinically significant’ or ‘abnormal, clinically significant’. A shift table will be produced showing the categories at screening against those during treatment period (after first IMP dosing, before and after last IMP dosing) by treatment. Another shift table will be presented showing the categories prior to last IMP administration against those after last IMP administration by treatment.

Subjects with abnormal ECGs will be listed as evaluated by the investigator or by the central lab.

14.3.9.5 Clinical laboratory evaluation

The descriptive statistics arithmetic and geometric mean, SD, median, minimum, and maximum values will be provided for each of the laboratory parameters at screening (visit 1), at the end of each treatment period (visit 3 and visit 5, respectively) and at the end of the follow-up period (visit 6) by treatment sequence.

Similar tables will also be provided for each of the laboratory parameters at screening (visit 1) and at the end of the treatment periods (visit 3, visit 5 respectively) by treatment. In addition, the change in each of the laboratory parameters from baseline to the end of treatment period will be included in the tabular display. Baseline will be the last value during screening period.

Laboratory parameters will be classified as 'low', 'normal' or 'high', depending on whether the value is below, within, or above the reference range, respectively. A shift table will be produced showing the categories at baseline against those at the end of the treatment period by treatment. Baseline will be the last value during screening period. Subjects with laboratory parameters outside the reference range will be listed.

14.3.10 Pharmacokinetic analysis

The analysis of PK will be based on the PK analysis set.

To analyse systemic exposure of LEO 152020 the following PK parameters will be calculated after first dose of each treatment period (visit 2 and visit 4 or 4a, respectively) and pre- and post-dose at the end of each treatment period (visit 3 and visit 5, respectively): AUC_{0-t}, AUC_{0-inf}, C_{max}, t_{max} and $t_{1/2}$.

For PK drug concentrations measured at visits 2-5, arithmetic and geometric mean, SD, coefficient of variation (CV), median, minimum and maximum values will be provided by visit.

14.3.11 Interim analysis

No interim analysis is planned.

14.3.12 General principles

All significance tests will be two-sided using the 5% significance level. All confidence intervals will be presented with 95% degree of confidence, unless otherwise specified.

All the analyses specified in the protocol will be reviewed in relation to the blinded data actually obtained and the statistical analysis plan will be finalised before the unblinding.

Any changes from the statistical analyses planned in this clinical trial protocol will be described and justified in a protocol amendment and/or the statistical analysis plan and/or in the CTR, dependent on the type of change.

14.3.13 Handling of missing values

In case a subject permanently discontinued IMP during a treatment period the early termination visit will be taken for the end of treatment visit. This applies for the investigator measurements UASprovo (including time to sweating and time to whealing) and the lab parameters of serum chemistry and haematology.

Concerning the analysis of the primary efficacy endpoint, the baseline value of the corresponding treatment period will be carried forward, if the value at end of treatment period is not available. No imputation will be performed when the baseline value is not available.

A sensitivity analysis will be performed for the primary endpoint based on subjects from the FAS with values available at baseline as well as at the end of the treatment period for both periods (complete cases analysis).

For secondary / exploratory endpoints of efficacy, no imputation of missing values will be performed.

Sum scores are only derived if all item scores are available.

CholUAS-7 score will only be calculated when the wheals (hives) severity score and the itch severity score (ISS) for the last seven days are available: If a subject has at least 5 available daily scores within the 7 days prior to the study visit, the weekly score is calculated as the sum of the available daily scores in that week, divided by the number of days with available score multiplied by 7. If there are less than 5 available daily scores within the 7 days prior to the study visit, then the weekly score is missing for this week.

Missing values of safety parameters will generally be treated as such and will not be replaced.

15 References

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Appendix 1: Definitions of adverse events and serious adverse events

Adverse event definition

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. [35]

This definition includes:

- Accidental injuries.
- Events related to trial procedures.
- Reasons for any unfavourable and unplanned change in medication (drug and/or dose).
- Clinically significant worsening of pre-existing conditions.
- Reasons for admission to hospital or surgical procedures unless these were planned before the subject consented to trial participation.
- AEs commonly observed and AEs anticipated based on the pharmacological effect of the IMP.
- Any laboratory abnormality assessed as clinically significant by the investigator (see Section 11.4.4.2).

Serious adverse event definition

An SAE is any untoward medical occurrence that:

- Results in death.
- Is life-threatening – at risk of death at the time of the SAE (not an event that hypothetically might have caused death if more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization*.
- Results in persistent or significant disability/incapacity.

- Is a congenital anomaly/birth defect.
- Is a medically important condition. Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, and convulsions that do not result in hospitalisation, development of drug dependency, or drug abuse.

Additionally, all malignancies, incl. skin malignancies, should be reported as SAEs.

*Hospitalization for procedures or treatments planned prior to the subject consented to trial participation does not constitute an AE and should therefore not be reported as AE or SAE.

Hospitalization for elective treatment of a pre-existing condition which did not worsen from the subject consented to trial participation is not considered an AE and should therefore not be reported as AE or SAE, even if not planned before consent to trial participation.

Hospitalization for routine scheduled treatment or monitoring not associated with any aggravation of the condition does not constitute an AE and should therefore not be reported as AE or SAE.

Hospitalization for administrative purpose does not constitute an AE and should therefore not be reported as AE or SAE.

Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization, the event is an SAE.

When in doubt as to whether hospitalization occurred, the AE should be considered serious.

Definition of adverse events of special interest

An AESI (serious or non-serious) is an event type of scientific and medical concerns specific to the product or development program, for which additional monitoring may be appropriate. Such an event might warrant further investigation in order to characterise and understand it. Depending on the nature of the event, rapid communication by the investigator to the sponsor and/or from the sponsor to other parties (e.g. regulators) might also be warranted.

AESIs are described in Section 13.5.2 and Section 13.6.1.

Appendix 2: Classification of adverse events

Severity

The *severity* of the AE should be described in terms of mild, moderate, or severe according to the investigator's clinical judgement.

Mild	An AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	An AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	An AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

If the severity of an AE worsens, a new AE should be recorded.

Causality

The *causal relation* of the AE to the use of the IMP should be described in terms of probably, possibly, or not related according to the investigator's clinical judgement.

Probably related	Follows a reasonable temporal sequence from administration of the IMP. Could not be reasonably explained by the subject's clinical state, environmental or toxic factors or other therapies administered to the subject. Follows a known pattern of response to the IMP. Disappears or decreases on cessation or reduction in dose of the IMP. Reappears or worsens upon re-challenge.

Possibly related	Follows a reasonable temporal sequence from the administration of the IMP. Could also be reasonably explained by the subject's clinical state, environmental or toxic factors or other therapies administered to the subject. Follows a known pattern of response to the IMP.
Not related	Does not follow a reasonable temporal sequence from administration of the IMP. Is better explained by other factors like the subject's clinical state, environmental or toxic factors or other therapies administered to the subject. Does not reappear or worsen upon re-challenge. Does not follow a known pattern of response to the IMP.

Outcome

The *outcome* of the event according to the investigator's clinical judgement should be classified using the categories below.

Recovered/ resolved	The event has stopped. The stop date of the event must be recorded.
Recovering/ resolving	The subject is clearly recovering from an event. The event is not yet completely resolved.
Not recovered/ not resolved	Event is still ongoing.
Recovered/ resolved with sequelae	The event has reached a state where no further changes are expected and the residual symptoms are assumed to persist. An example is hemiparesis after stroke. The stop date of the event must be recorded. In case of a SAE, the sequelae should be specified.
Fatal	The subject has died as a consequence of the event. Date of death is recorded as stop date for the AE.
Unknown	Unknown to investigator, e.g. subject lost to follow-up.

LEO Pharma definitions versus CDISC definitions

Note that as per the above definition, LEO Pharma uses “recovered/resolved” only if an event has actually stopped. According to the CDISC definition, the category “recovered/resolved” also includes events which have improved. However, following the LEO Pharma definitions above, such an improved event will instead be classified as “not recovered/not resolved” or “recovering/resolving”.

Similarly, it should be noted that as per the above definition, LEO Pharma uses “recovered/resolved with sequelae” only if an event has reached a state where the residual symptoms are assumed to persist. According to CDISC, an event is considered “with sequelae”, if it has “retained pathological conditions”. Consequently, it is likely that some of the events classified by LEO Pharma with the outcome “recovered/resolved with sequelae” could have been classified with the outcome “recovered/resolved” according to the CDISC definition.

In summary, the definitions used by LEO Pharma are more conservative than those used by CDISC.

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Appendix 3: Trial governance considerations

Appendix 3A: Regulatory and ethical considerations

This trial will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the current version of the Declaration of Helsinki [18] and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines [38].
- Current version of applicable International Council for Harmonisation Good Clinical Practice (ICH GCP) Guidelines [39].
- EU General Data Protection Regulation 2016/679 of 27 April 2016.
- Applicable laws and regulations.

The German regulatory authority must approve the clinical trial as required.

Any documents that the IRB/IEC may need to fulfil its responsibilities (such as the trial protocol, protocol amendments, investigator's brochure [as applicable], subject information sheet, and informed consent form(s), or advertisements) will be submitted to the IRB/IEC. These documents must be reviewed and approved by the IRB/IEC before the trial is initiated.

Any amendments to the protocol must be approved by/receive favourable opinion from German regulatory authority and IRBs/IECs, as required, prior to implementation.

The principal investigator will be responsible for the following, if required by local legislation:

- Providing written summaries of the status of the trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the local IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the trial at the trial site and ensuring adherence to applicable national and international legislation.

Appendix 3B: Informed consent process

Subjects will receive written and verbal information concerning the clinical trial. This information will emphasise that participation in the clinical trial is voluntary and that the subject may withdraw from the clinical trial at any time and for any reason. All subjects will be given an opportunity to ask questions and will be given sufficient time to consider before consenting.

The subject's signed and dated informed consent to participate in the clinical trial will be obtained prior to any clinical trial-related procedure being carried out in accordance with ICH GCP and all applicable laws and regulations. The authorised person obtaining the informed consent must also sign the ICF.

Subjects will be re-consented to the most current version of the ICF(s) during their participation in the trial, if required.

A copy of the ICF(s) must be provided to the subject.

Subject card
At randomisation, subjects will be provided with a card stating that they are participating in a clinical trial and which contains contact address and telephone number(s) of relevant trial site staff including the number for the investigator in case of emergency situations. The subject card also includes subject's randomisation code number and a local telephone number for the emergency unblinding CRO to be used if the investigator or delegated site staff cannot be reached.

Appendix 3C: Subject and data confidentiality

This clinical trial protocol as well as all other information, data, and results relating to this clinical trial and/or to the IMP is confidential information of LEO Pharma and shall not be used by the investigator for purposes other than this clinical trial.

The investigator agrees that LEO Pharma may use any and all information, data, and results from this clinical trial in connection with the development of the IMPs and, therefore, may disclose and/or transfer information, data and/or results to other investigators, regulatory authorities, and/or commercial partners.

Trial subjects will be assigned a unique identifier (subject ID) by LEO Pharma. Any subject's records or datasets that are transferred to LEO Pharma will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

Trial subjects must be informed that their personal trial-related data will be used by LEO Pharma in accordance with local data protection law.

Trial subjects must be informed and consent to that their medical records may be examined by clinical quality assurance auditors or other authorised personnel appointed by LEO Pharma, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Trial subjects must be informed that LEO Pharma might keep their trial-related data for as long as they are useful for developing treatments for the disease or other diseases and future research.

Processing of personal data
This protocol specifies the personal data on trial subjects (for example race, ethnicity, age, gender, health condition, medical history, test results, etc.) which shall be collected as part of the clinical trial and processed during and after trial completion.

Personal data collected as part of the clinical trial will be transferred to/from the institution/investigator, LEO Pharma, and third parties acting on behalf of LEO Pharma.

Processing of personal data on behalf of LEO Pharma requires a written agreement between LEO Pharma and the relevant party which covers collection, processing, and transfer of personal data in the clinical trial. In certain cases, an agreement on transfer of personal data may also be required.

Investigators and LEO Pharma must ensure that collection, processing and transfer of personal data are in compliance with applicable legislation on data protection and privacy, including but not limited to the EU General Data Privacy Regulation.

Subjects must be asked to consent to the collection, processing, and transfer of their personal data to EU and non-EU countries for the purpose of conducting the clinical trial, research and development of new or existing products/services, improving existing products/services, applying for marketing authorisations for products/services, marketing of products/services and other related activities.

LEO Pharma has obtained the necessary authorisations for the processing of personal data collected in the trial.

Appendix 3D: Record keeping, quality control, and data handling

Source data at trial sites

For all data recorded, the source document must be defined in a source document agreement or similar document at each trial site. There must only be 1 source defined at any time for any data elements.

Source data should as a general rule be recorded in the subject's medical record or other defined document normally used at the trial site. Source data not normally collected as a routine part of the clinical practice at the site may be entered on a worksheet. Clinical assessments/safety evaluations must be signed and dated by medically qualified investigators.

If the worksheet does not become part of the subject's medical record, the following should as a minimum be added to the subject's medical record:

- Subject ID.
- Randomisation code number.
- The fact that the subject is participating in a clinical trial in cholinergic urticaria including treatment with LEO 152020 and placebo for up to 6 weeks.
- Other relevant medical information.

Trial monitoring

During the course of the trial, CRA(s) will visit the trial site. These visits have the following objectives: (i) to continually verify source data to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; (ii) to confirm that the safety and rights of subjects are being protected; and (iii) to confirm that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

A risk-based monitoring approach will be applied. The monitoring visit intervals will depend on the trial site's recruitment rate and the compliance of the trial site with the protocol and ICH GCP. The level of source data verification, data checks, and visit intervals will be specified in the monitoring guideline.

In addition to on-site monitoring, pre-specified trial data will undergo central monitoring as specified in the trial's data review plan.

In order to perform their role effectively, CRAs and persons involved in quality assurance and inspections will need direct access to source data, for example, medical records, laboratory

reports, appointment books, etc. If the electronic medical record does not have a visible audit trail, the investigator must provide the CRA with signed and dated printouts. In addition, relevant site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).

Protocol compliance
Protocol deviations will be documented and notified to the investigator. Protocol deviations will be assessed by LEO Pharma and major deviations described in the CTR.

Sponsor audits, IRB/IEC review, and regulatory agency inspections
The clinical trial will be subject to audits conducted by LEO Pharma or inspections from domestic or foreign regulatory authorities or from IRBs/IECs. Audits and inspections may take place during or after the trial. The investigator and the site staff as well as LEO Pharma staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial. This includes permission to examine, verify, and reproduce any records and reports that are important to the evaluation of the trial.

If the trial site is contacted for an inspection by competent authorities, LEO Pharma must be notified immediately.

Data handling
Data will be collected by means of electronic data capture unless transmitted electronically to LEO Pharma or designee (e.g., laboratory data). The investigator or staff authorised by the investigator will enter subject data into electronic CRFs (eCRF). Data recorded in the eCRF will be accessible to the trial site and LEO Pharma personnel immediately after entry. The eCRF must be maintained in an up-to-date state by the trial site at all times.
The investigator must verify the correctness of the data entered by the site by electronically dating and signing all eCRF used. This signature information will be kept in the audit trail and cannot be altered. Any correction(s) made by the investigator or authorised site staff to the eCRF after original entry will be documented in the audit trail. Changes to data already approved will require re-signature by the investigator. The person making the change to the data, and the date, time, and reason for the change will be identified in the audit trail.

Subject data should be entered into the eCRF no later than 5 working days after each visit, unless a different deadline is stated in the clinical trial agreement. Queries for discrepant data will be generated automatically by the system upon entry or manually by the CRA, sponsor’s medical expert, or the data manager. All queries will be raised electronically within the

electronic data capture system. This systematic validation will ensure that a clean and consistent database is provided for the statistical analysis.

External data transfers from vendors to LEO Pharma will be transmitted and handled via a secure file transfer protocol site.

Transmissions of data are documented in more detail in appropriate plans such data management plan which is part of the trial master file.

Used standards

CDISC controlled terminology version 06-Nov-2020 was used for definition of controlled terminology used throughout this protocol and will be used for statistical programming and output. SDTM version 1.7 will be used for data tabulations.

Archiving of trial documentation

The investigator at each trial site must make arrangements to store the essential trial documents, including the investigator trial file [39]. Essential trial documents must be stored until LEO Pharma informs the investigator that the documents are no longer to be retained, or longer if required by local regulations.

In addition, the investigator is responsible for the archiving of all relevant source documents so that the trial data can be compared against source data after the completion of the trial (for example in case of an inspection from regulatory authorities).

The investigator is required to ensure the continued storage of the documents even if the investigator leaves the trial site or retires before the end of the required storage period.

No documents may be destroyed during the retention period without the written approval of LEO Pharma. No documents may be transferred to another location or party without written acceptance from LEO Pharma.

The destruction process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

For archiving purposes, each investigator will be supplied with an electronic copy of the eCRFs for all screened subjects at the trial site. This is done after completion of the trial and before access to the eCRF is revoked. Audit trail information will be included. eCRFs must be available for inspection by authorised representatives from LEO Pharma, from regulatory authorities and/or IRBs/ IECs.

Appendix 3E: Registration, reporting and publication policy

Trial disclosure

LEO Pharma is committed to be transparent with respect to its clinical trials.

Basic information of this clinical trial will be registered in the global data registry, www.ClinicalTrials.gov before the first subject enters into the trial. The trial may also become registered in other online data registries, according to applicable law and regulations.

Results of this clinical trial will be posted on the corporate website of LEO Pharma in accordance with our Position on Public Access to Clinical Trial Information no later than 12 months after trial completion. Trial results may also become reported in www.ClinicalTrials.gov, www.clinicaltrialsregister.eu and national data registries in accordance with applicable law and regulations after clinical trial completion or premature termination.

LEO Pharma may also provide researchers access to anonymised patient-level data for further research. Publication and access will be in accordance with the Position on Public Access to Clinical Trials which can be found on the LEO Pharma website. Moreover, LEO Pharma may re-use the same patient-level data for other projects within the same purpose as the trial.

Publications

The investigator shall be entitled to make publications of the results generated by the investigator in accordance with the process described here.

A multi-site publication will be submitted for publication within 18 months after the clinical trial has been completed or terminated at all trial sites and all data have been received, defined as database lock of the clinical trial. After such multi-site publication is made public, or if no multi-site publication has been submitted with the above-described deadline, the investigator shall have the right to publish the results from the clinical trial generated by the investigator, subject to the following notice requirements:

Prior to submission for publication or presenting a manuscript relating to the clinical trial, the investigator shall provide to LEO Pharma a copy of all such manuscripts and/or presentations. LEO Pharma shall have rights to review and comment. The investigator shall consider comments provided by LEO Pharma but is not required to modify the manuscript and/or presentation based on such comments, provided, however, that the investigator upon the request of LEO Pharma remove any confidential information (other than results generated by the investigator) prior to submitting or presenting the manuscripts. The investigator shall,

upon the request of LEO Pharma withhold the publication or presentation to allow LEO to protect its inventions and other intellectual property rights described in any such manuscripts.

In case no multi-site publication has been made public at the time of investigator's notification of an independent publication to LEO Pharma, LEO Pharma and the writing group may also delay the publication or presentation if the manuscript is deemed to harm the ongoing multi-site publication.

In case of publications made by the investigator after the first multi-site publication has been published, the above-mentioned requirements must still be followed.

Any publication must comply with Good Publication Practice (GPP3) standards.

LEO Pharma complies with GPP3 standards and the recommendations from the International Committee of Medical Journal Editors. LEO Pharma complies with the positions of the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), European Federation of Pharmaceutical Industries and Associations (EFPIA), Japan Pharmaceutical Manufacturers Association (JPMA), Pharmaceutical Research and Manufacturers of America (PhRMA), and the joint position statement by the American Medical Writers Association (AMWA), the European Medical Writers Association (EMWA), and the International Society for Medical Publication Professionals (ISMPP) on disclosure of information about clinical trials, trial results and authorship. LEO Pharma also follows the CONSORT reporting guidelines [40].

Appendix 3F: Insurance

LEO Pharma has taken out relevant insurances covering the subjects in the present clinical trial in accordance with applicable laws and regulations.

Appendix 3G: Financial disclosure

Investigators will provide LEO Pharma with sufficient, accurate financial information as requested to allow LEO Pharma to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the clinical trial and for 1 year after completion of the clinical trial, or for a longer period of time if required by local legislation.

Appendix 3H: Trial and trial site closure

Premature termination of trial or trial site

LEO Pharma, the investigator, the IRB/IECs or competent authorities may decide to stop the clinical trial, part of the trial or a trial site at any time, but agreement on procedures to be followed must be obtained.

If a clinical trial is suspended or prematurely terminated, the investigator must inform the subjects promptly and ensure appropriate therapy and follow-up. As specified by applicable regulatory requirements, the investigator or LEO Pharma must promptly inform IRB/IECs and provide a detailed written explanation. Relevant competent authorities must be informed.

The trial must be terminated if the perception of the benefit/risk ratio (judged from clinical signs and symptoms, (S)AEs and/or remarkable safety laboratory changes) becomes unfavourable for the continuation of the trial.

Reasons for the early closure of a trial site by LEO Pharma or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, LEO Pharma procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the investigator.

Completion of trial

Investigators will be informed when subject recruitment is to cease. Screening activities will be stopped at a trial site when the total requested number of subjects for the clinical trial has been obtained, irrespective of the specific site's planned inclusion number.

Trial sites will be closed upon trial completion. LEO Pharma will undertake arrangements for the collection and disposal of any unused trial material that the investigator is not required to keep in his/her files. A trial site is considered closed when all required documents and trial supplies have been collected and a trial site closure visit has been performed.

When the randomisation code has been broken, the investigators will receive information about the treatment allocation for the subjects randomised at their respective sites and will be asked to record this in the subject's medical record.

Appendix 3I: Responsibilities

The signatory investigator is responsible for the approval of the clinical trial protocol and the CTR on behalf of all clinical trial investigators and as agreed to in a signatory investigator agreement.

Each participating investigator is responsible for all aspects of the clinical trial conduct at his/her trial site as agreed to in a clinical trial agreement.

Appendix 4: Examples of prohibited medication

Medication known to inhibit the BCRP transporter • Bempedoic acid • Obeticholic acid • Telmisartan • Teriflunomide	Within 5 half-lives prior to baseline until Safety follow-up
Medications known to inhibit the P-gp transporter	Within 5 half-lives prior to baseline until Safety follow-up
• Amiodarone • Amlodipine • Atorvastatin (acid) • Azithromycin • Baloxavir marboxil • Bitopeectin • Canagliflozin • Carvedilol • Cefuroxime • Cetirizine • Clarithromycin • Diltiazem • Dronedarone • Elagolix • Erythromycin • Flibanserin • Fluvoxamine • Fostamatinib • Isavuconazole • Istradefylline • Itraconazole • Ivacaflor • Ketoconazole • Maribavir • Methadone	

• Mirabegron • Naproxen • Nefazodone • Nystatin • Omeprazole • Pantoprazole • Paroxetine • Pilsicainide • Posaconazole • Praziquantel • Propafenone • Quinidine • Ranolazine • Rifampin • Risperidone • Rolapitant • Sarecycline • Suvorexant • Talinolol • Telithromycin • Tezacaftor • Ticagrelon • Tolvaptan • Valbenazine • Verapamil • Vorapaxor • Voriconazole	
Medication known to inhibit the OAT3 • Probenecid	Within 5 half-lives prior to baseline until Safety follow-up

Appendix 5: Short version of eligibility criteria

Inclusion criteria	
No.	**Short version**
1	Signed and dated informed consent
2	Subject with a history of CholU diagnosis for ≥ 6 months
3	Subject has active and uncontrolled CholU disease at the time of screening and randomisation, as defined by the following: a. Urticaria control test (UCT) < 12 at screening b. UASprovo ≥ 3 (with a minimum wheal score of ≥ 1 and minimum itch score of ≥ 1) at screening* and randomisation. *Screening provocation test is optional if patients had a prior provocation test that met threshold within 6 months of day 1 (visit 2)
4	Subjects aged ≥ 18 years
5	Subjects must not have more than one missing diary entry in the 7 days prior to randomisation.
6	Recent history CholU diagnosis (within 6 months) with documented inadequate response to standard dose as to marketing authorization H1 antihistamines
7	Female subjects of childbearing potential must use a double contraception (highly effective plus barrier forms) of contraception from screening until the end of the trial (safety follow up visit).
8	Male subjects with a female partner of child-bearing potential must use adequate double contraceptive methods (barrier from in conjunction with a highly effective form of female contraception for the partner) from randomisation to safety follow-up visit.
Exclusion criteria	
No.	**Short version**
1	Other forms of clearly dominating urticaria as aetiology for wheal and flare type reactions, including: a. Chronic spontaneous urticaria b. Inducible urticaria: urticaria factitia / symptomatic dermographism, cold-, heat-, solar-, pressure-, vibratory-, aquagenic-, or contact-urticaria Note: The other forms of diseases mentioned above are allowed as comorbidities, if <u>cholinergic urticaria</u> is the <u>dominating form</u> of chronic urticaria
2	Clinically significant infection within 4 weeks prior to randomisation that may compromise the safety of the subject
3	History of lymphoproliferative disease or any known or history of malignancy within the past 5 years
4	Risk factors for Torsades de Pointe including a. Uncorrected hypokalemia, hypocalcemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia b. (Congenital) long QT syndrome or family history of idiopathic sudden death c. Concomitant medication(s) with a known risk of Torsades de Pointe d. Other cardiac arrhythmia risk factors at the discretion of the investigator

5	Concomitant drugs with known prolongation of QT interval within 5 half-lives prior to screening
6	Resting QTcF (average of a triplicate measurement) < 300 msec or > 450 msec at screening
7	Known history of ventricular arrhythmias
8	Second- and third-degree atrioventricula block
9	Subjects with signs of renal impairment as determined by eGFR levels below 90 mL/min at screening
10	Subjects with signs of hepatic impairment as determined by abnormal liver function tests, defined as total bilirubin, aspartate aminotransferase or alanine aminotransferase >1.5 x the upper limit of normal (ULN) range, at screening
11	Infection with human immunodeficiency virus (HIV)
12	Presence of hepatitis B or C infection
13	Subjects with confirmed active infection with SARS-CoV-2 AND related COVID-19 symptoms, which at the discretion of the investigator will jeopardize the safety of the subject or the integrity of the data collected. Additionally, any local requirements must be followed.
14	Any medication known to chronically alter drug absorption or elimination processes within 30 days prior to the first dose of IMP
15	Systemic immunosuppressive medications within 4 weeks prior to screening
16	Systemic corticosteroids within 4 weeks prior to screening and throughout the trial (except for inhaled or intranasal steroids equivalent to doses up to 1 mg prednisone daily)
17	Drugs which are known inhibitors of the P-gp and BCRP transporters and the strong OAT3 inhibitor probenecid within 1 weeks prior to randomisation or 5 half-lives (whichever is longer)
18	Systemic drugs (e.g. oral drug) with antihistamine properties including H1 antihistamines and some antidepressants (e.g. tricyclic antidepressants) and H2 antihistamines 1 week prior to randomization. However, topical antihistamines in the form of nasal spray and eyedrops are allowed in the standard prescribed dose.
19	Use of tanning beds or phototherapy within 4 weeks of screening
20	Known or suspected hypersensitivity to any component(s) of the IMP
21	Known hypersensitivity to iodine
22	Current participation in any other interventional clinical trial
23	Treatment with any non-marketed drug substance within last 3 months
24	Previous randomisation in this trial.
25	History of chronic alcohol or drug abuse within 12 months
26	Any subject dependent from trial site, sponsor or subcontractors
27	Subjects who are legally institutionalised
28	Female subject who are pregnant or lactating
29	Any unstable medical, surgical, psychiatric, or additional physical disorder which according to investigator's opinion could

	• Affect subject safety and well-being • Influence the findings of the trial. • Impede the subject's ability to complete the trial.
30	Any clinically significant abnormal finding at screening and/or baseline which according to investigator's opinion may • Affect subject safety and well-being • Influence the findings of the trial or subject's ability to complete the trial.

Appendix 6: Contact list

Contact details for the CPM, appointed CRA, and sponsor's medical expert are provided to the trial sites as a separate contact list.

Sponsor

LEO Pharma A/S (referred to as 'LEO Pharma' or 'the sponsor' in this clinical trial protocol) is the sponsor of the clinical trial:

LEO Pharma A/S
Industriparken 55
DK-2750 Ballerup
Denmark

Coordinating investigator

PPD

Germany

Appendix 7: Protocol amendment history

Amendment 5 (09-Mar-2022)

This amendment is considered substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union or subsequent regulation.

Overall rationale for the amendment:

Due to a change of location and the new foundation of the PPD under the direction of PPD and PPD, the contact details of the Coordinating Investigator have changed and have been updated with this amendment. Furthermore, this amendment takes into account the change of the statistician.

Section no. and name	Description of change	Brief rationale
1. Protocol synopsis **Appendix 6: Contact List**	**Change of contact details for the Signatory Investigator (Coordinating Investigator):** Formerly: PPD New: PPD Germany	**Change of address**

Section no. and name	Description of change	Brief rationale
Clinical trial protocol statements	PPD **has been replaced by** PPD**, the new lead statistician at LEO Pharma A/S**	**Due to personnel changes and changes in project responsibility at LEO Pharma A/S, it is necessary to adapt the Approval Statement accordingly**

Amendment 4 (06-Dec-2021)

This amendment is considered non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union or subsequent regulation.

Overall rationale for the amendment:

Contact details of LEO Global Drug Safety have been updated

Section no. and name	**Description of change**	**Brief rationale**
9.10 Reporting Product Complaints **13.4.1 Investigator Reporting Responsibilities**	**New Fax Number added:** Global Safety at LEO Pharma E-mail address: drug.safety@leo-pharma.com Fax number: ~~+45 7226 3287~~ +45 6910 2468	**Change of Fax Number**

Amendment 3 (15-Jun-2021)

This amendment is considered substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union or subsequent regulation.

Overall rationale for the amendment:

As patients with cholinergic urticaria belong to a group of patients with a general predisposition to allergies, exclusion criterion 18 was changed to obtain a study population as representative as possible and to support recruitment by allowing patients to continue topical use of antihistamines if necessary to treat concomitant allergies.

Section no. and name	**Description of change**	**Brief rationale**
1 Protocol synopsis 8.3 Exclusion criteria Appendix 5 Short version of eligibility criteria	Exclusion criterion 18 has been rephrased as follows, allowing previous or concomitant treatment with topical antihistamines. From: Drugs with antihistamine properties including H1 antihistamines and some antidepressants (e.g. tricyclic antidepressants) and H2 antihistamines 1 week prior to randomisation and throughout the trial. To: ***Systemic*** drugs ***(e.g. oral drug)*** with antihistamine properties including H1 antihistamines and some antidepressants (e.g. tricyclic antidepressants) and	After recruitment of the first patients with cholinergic urticaria, it became apparent that a general prohibition of antihistamines would significantly limit the inclusion of a representative study population characterised by a general predisposition to allergies. As systemic availability of antihistamines after topical application is considered negligible, it was decided to allow the use of topical antihistamines (e.g. nasal sprays and eye drops) for the treatment of concomitant allergies (e.g. allergic rhinitis or hay fever), if applied in the standard prescribed dose.

Section no. and name	Description of change	Brief rationale
	H2 antihistamines 1 week prior to randomisation and throughout the trial. ***However, topical antihistamines in the form of nasal spray and eyedrops are allowed in the standard prescribed dose.***	
4 Schedule of trial procedures 7.1.1 Screening phase	In line with the permission to continue treatment with topical antihistamines in the standard prescribed dose, the corresponding footnote in the schedule of study procedures (section 4) and the note on adherence to a 1-week washout period for antihistamines and/or medications with antihistamine properties in the description of the screening procedures (section 7.1.1) have been updated accordingly.	
9.7 Prohibited medication(s) and procedures	With the permission to continue treatment with topical antihistamines, it also became necessary to adapt panel 5 by introducing a note for H1 antihistamines indicating that treatment with topical antihistamines will be allowed throughout the study if used in the standard prescribed dose.	

Section no. and name	**Description of change**	**Brief rationale**
Approval statement LEO Pharma A/S	The position of the medical lead has been changed from "Medical Sciences" to "Translational Medicine, Research & Early Development".	With the last Amendment (Amendment 2, dated 16-Apr-2021) PPD has been introduced as new medical lead. Due to internal reorganisation at LEO Pharma A/S, the position of the medical lead has changed and has now been adjusted accordingly in the Approval Statement.
All sections	Correction of typos and grammatical errors throughout the protocol.	Not applicable

Amendment 2 (16-Apr-2021)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union or subsequent regulation because it neither significantly impacts the safety or physical/mental integrity of subjects nor the scientific value of the trial.

Overall rationale for the amendment:

The general study procedures, objectives, methods etc. are NOT altered; also, the in- and exclusion criteria are NOT changed. In those respects, Clinical Trial Protocol, version (Amendment 1) remains valid - with the corrections presented here.

However, some inconsistencies and/or imprecision render an update of those passages necessary to clarify the intent of the original protocol. Furthermore, the Approval Statement needed to be updated due to personnel changes at LEO Pharma A/S.

Section no. and name	Description of change	Brief rationale
4 Schedule of trial procedures	A footnote has been added to the screening phase referring to the need for a 7 days screening period in minimum to ensure to ensure a 7-day documentation of the ChloUAS (in the patient's diary) for calculation of the CholUAS7 at baseline visit (visit 2), and if applicable to respect a) a minimum interval of 7 days between two UAS provocation tests and/or ,b) a 1-week washout period for antihistamines and/or medications with antihistamine properties.	In order to emphasise that a minimum screening period of 7 days is required, i.e. that the screening visit (visit 1) must be carried out at least 7 days before the baseline visit (visit 2) to allow all study procedures to be carried out in accordance with the protocol before randomisation, it was considered necessary to add this information explicitly.

Section no. and name	Description of change	Brief rationale
7.1.1 Screening phase	To further describe that the patient's diary must be handed over 7 days prior to the baseline visit at the latest, this information was added to section 7.1.1 providing an overview regarding the activities to be performed during the screening phase.	
4 Schedule of trial procedures 7.1.3 Visit 6 – Safety Follow-up	In footnote 1, information was added that the early termination (ET) visit (in addition to the safety follow-up visit) should be conducted as soon as possible after the last administration of the IMP to obtain a final efficacy assessment. Furthermore, it was clarified that no ET-visit needs to be conducted if this visit cannot be scheduled within a maximum of 3 days after the last administration of the IMP. In this latter case, every effort should be done to perform the regular safety follow-up (visit 6) as the last visit. The phrase "early termination / end of study visit" was changed to "early termination /	During the development of the eCRF, it became apparent that the description of the visits to be conducted in the event of early withdrawal from the trial and the timing of their conduct were not entirely clear. It was therefore deemed necessary to amend the description of the respective visits accordingly and to further clarify that the ET-visit is primarily to obtain a final efficacy assessment, while the follow-up visit (regular visit 6) aims to ensure patient's safety.

Section no. and name	Description of change	Brief rationale
10.3 Early termination assessments	end of treatment visit" to make sure that the ET-visit is to be performed as soon as possible after the last administration of the IMP. To be precise and to provide clear instructions, the information on the time frame for conducting the ET-visit and/or the safety follow-up visit (visit 6) has been revised.	
9.8.2 Storage of Trial Products	The reference to higher storage temperatures than those indicated on the label of the IMP has been deleted.	To be consistent with the labelling of the IMP, it became necessary to delete the reference in regard to possibly higher storage temperatures of the IMP.
11.3.4.2 Urticaria Control Test	The individual ratings for the response options for the 4 questions of the Urticaria Control Test (UCT) have been added in Panel 7.	For reasons of clarity, the response options to each of the 4 questions of the UCT in Panel 7 were supplemented by their individual rating on a scale from 0 to 4.
11.3.4.3 Cholinergic Urticaria Activity Score 7	The description of the Cholinergic Urticaria Activity Score 7 (CholUAS7) has been updated to correctly reflect that this validated questionnaire consists of a total of 4 questions.	During the final reconciliation between the protocol and the eCRF/patient diary, it was noticed that the description of the CholUAS7 in the original protocol was not completely correct, as the CholUAS7 questionnaire consists of a total of 4 questions and not of only 2 questions regarding the severity of hives and itching. Therefore, it was necessary to

Section no. and name	Description of change	Brief rationale
		correct the description of the CholUAS7 accordingly.
Appendix 7 Protocol Amendment History	Newly added section, describing the changes implemented with Amendment 1 (protocol version 2.0, dated 09-Mar-2021).	According to LEO SOPs it became necessary to add an additional Appendix, to reflect the changes implemented with the first Amendment, which became necessary in order to take account of objections raised by the BfArM (Federal Institute for Drugs and Medical Devices; German Regulatory Authority [RA]) and by the LAGeSo Berlin (Regional Office for Health and Social Affairs Berlin), the relevant German Ethics Committee (EC).
Approval statement LEO Pharma A/S	1) The lead in biostatistics was taken over by PPD 2) The medical lead was taken over by PPD	Due to personnel changes and changes in project responsibility at LEO Pharma A/S, it is necessary to adapt the Approval Statement accordingly
All sections	Correction of typos and grammatical errors throughout the protocol.	Not applicable

Amendment 1 (09-Mar-2021)

This amendment is considered substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union or subsequent regulation.

Overall rationale for the amendment:

The Clinical Trial Protocol Version 2.0 became necessary in order to take account of objections raised by the BfArM (Federal Institute for Drugs and Medical Devices; German Regulatory Authority [RA]) received on 26-February-2021 and by the LAGeSo Berlin (Regional Office for Health and Social Affairs Berlin), the relevant German Ethics Committee (EC) received on 24-February-2021.

Section no. and name	**Description of change**	**Brief rationale**
Synopsis 8.2 Inclusion criteria 12.1 Scientific rationale for trial design Appendix 5	To be unambiguous, “standard dose” in inclusion criterion #6 has been defined as dose according to marketing authorization. The same definition for “standard dose” was in addition introduced in regard to the description of the trial population intended to be included into this trial as given in section 12.1 of the CTP. Short version of eligibility criteria was updated accordingly.	The Regulatory Authority has asked to clarify whether the term "standard dose" of H1-antihistamines as used in EC#6 corresponds to a daily dose up to 4-fold higher than the licensed dose as recommended in the current guidelines. This would require an off-label use of respective drugs. Since the sponsor and the investigator are of the opinion that off-label use should not be part of an inclusion criterion, it has been clarified that the term “standard dose” is meant in the sense of the licensed dose.
8.2 Inclusion criteria	As a vasectomised partner is regarded as a highly effective birth control method only, if vasectomised partner is the sole sexual partner of the WOCBP	To be in line with HMA/CTFG Recommendations related to contraception and pregnancy testing, version 1.1, 2020-09-21 and as requested by the regulatory authority,

Section no. and name	**Description of change**	**Brief rationale**
	trial participant and if vasectomised partner has received medical assessment of the surgical success, medical assessment of surgical success has been added to inclusion criterion #7.	inclusion criterion #7 was updated accordingly.
8.3 Exclusion criteria 11.4.4 Laboratory testing Appendix 5	Hypocalcaemia was added to inclusion criteria #7 as another risk factor for Torsades de Pointe, that need to be taken into consideration. Total and free calcium (albumin-corrected) as well as magnesium were added as additional lab parameters. Short version of eligibility criteria was updated accordingly.	In agreement with the opinion of the Regulatory Authority, exclusion criterion #4 dealing with risk factors for Torsades de Pointe was updated including hypocalcaemia. Furthermore, the lab panel was accordingly updated in addition, as electrolyte imbalances are not necessarily accompanied with clinical symptoms.
4 Schedule of trial procedures	In line with the implementation of additional ECG measurements in patients presenting with a moderate post-dose QT-prolongation, the schedule of procedures was adapted accordingly, by adding an additional ECG at the safety follow-up. Furthermore, it is pointed out now that ECG measurement at visits has to be repeated in case that an ECG measurement indicates a post-dose QT-prolongation with a	To be in line with the ICH guideline E14, the criteria for discontinuation and withdrawal due to QT-prolongation was revised. The guideline only recommends a discontinuation if QTcF is equal or higher than 500 ms. To sufficiently ensure patients safety and well-being, additional ECG measures were implemented for patients presenting with a moderate post-dose QT-prolongation now.

Section no. and name	**Description of change**	**Brief rationale**
	QTcF of > 480 ms or a change in QTcF > 30 ms from baseline (pre-dose ECG).	
10.2.1 Reasons for permanent discontinuation of IMP	Discontinuation from treatment with IMP due to QT-prolongation has been changed from QTcF > 450 ms to QTcF > 500 ms or change in QTcF from baseline (pre-dose ECG) > 60 ms.	
11.4.3 ECG	The information that a subject should be discontinued from treatment with any clinically significant QT-prolongation, has been taken out and was replaced by the information that only subjects presenting with a severe QT prolongation (i.e. QTcF > 500 ms or a change in QTcF from baseline (pre-dose ECG) > 60 ms) should be discontinued from treatment and from the trial, if the severity of QT-prolongation has been confirmed by a second ECG. For subjects presenting with a moderate QT-prolongation (i.e. 480 ms < QTcF ≤ 500 ms or 30 ms < change in QTcF from baseline (pre-dose ECG) ≤ 60 ms) it is now	

Section no. and name	**Description of change**	**Brief rationale**
13.6.1 Adverse events of special interest	described, that the ECG should be repeated to confirm this QT-prolongation, but that subjects at investigator's discretion may continue with the trial and that an additional ECG must be done at the safety follow-up. The definition of the severity of the AESIs was detailed accordingly with the addition that moderate (grade 2) QT-prolongation includes 30 ms < change in QTcF from baseline (pre-dose ECG) ≤ 60 ms	
5.5 Benefit/Risk assessment	The potential benefit of a treatment with new LEO 152020 is now presented in the context of available therapeutic alternatives.	The Regulatory Authority raised the objection that a summary presentation that puts the scientific evidence of known/potential/expected benefit to the available therapeutic alternatives was missing in the CTP, as required according to the principles of EMA/CHMP/ICH/135/1995 ICH E6[R2] "GCP" sections 2.2 and 6.2.3.. To address this objection, a corresponding section has been added to section 5.5.
8.4 Screening and screen failures	The date of birth was replaced by the year of birth, respectively by subject's age.	The Regulatory Authority as well as the EC have pointed out that the documentation of the entire date of birth does not correspond to pseudonymization and is therefore not

Section no. and name	**Description of change**	**Brief rationale**
11.2.1 Demographics		permissible according to Art. 32 para. 1 a), Art. 5 para. 1 f) of Regulation (EU) 2016/679 (General Data Protection Regulation) and Sec. 40 para. 2a p. 2 Cf. 1b) - d) AMG. To comply with the required pseudonymization, the date of birth was replaced by the year of birth (age).
10.5 (added as new section) Criteria for the termination of the trial	To comply with legal requirements, the following sentence has been added to the new section 10.5: "The Sponsor, the signatory investigator, the IECs or regulatory authorities may decide to temporarily halt / suspend the trial, to stop the trial, parts of the trial or an investigational site at any time."	The Regulatory Authority requested to supplement the CTP with the information that the sponsor must stop or terminate the study, if the favorable opinion or the approval is revoked (acc. to Sec. 42a Par. 1, 2, 4a, icw 4 AMG). Outstanding information was added as requested.
10.5.1 (added as new section) Termination of the whole trial 10.5.2 (added as new section) Termination of the trial at an individual trial site	To comply with Sec. 40 Par. 1 S. 3 Cf. 2 AMG, a new section has been integrated in the CTP now, in which the reasons are specified, that may lead to the discontinuation of the whole trial or a single trial site, respectively.	The Regulatory Authority also raised the objection that compelling and sufficiently specified reasons for premature discontinuation of the complete trial were missing in the protocol. To overcome this objection corresponding reasons including specific clinically measurable parameters have been defined.

Section no. and name	**Description of change**	**Brief rationale**
4 Schedule of trial procedures	1: The footnote addressing the sampling times for the biomarker sampling was not consistent with the corresponding details as given in section 11.6.1. Correspondingly this footnote was corrected, now stating that serum sampling for biomarker analysis at baseline visits (i.e. V2 and V4/4a) should be taken prior to the intake of the IMP and sampling at the end of treatment visits (i.e. V3 and V5) for each of the treatment periods should be done after the IMP intake.	During the review of the amended protocol some inconsistencies have been detected, that were corrected beside the requests from RA and relevant EC, to be unambiguous throughout the protocol. These changes do not change the intent of the original CTP.
11.4.4. Laboratory testing	2: Regarding the lab panel (panel 10) it was overlooked, that there is the need to obtain the estimated glomerular filtration rate from the measurement of creatinine in order to check for exclusion criterion #9 (Subjects with signs of renal impairment as determined estimated glomerular filtration rate (eGFR) levels below 90 mL/min at screening). A corresponding footnote has now been added to the lab	

Section no. and name	**Description of change**	**Brief rationale**
Section 11.4.3 ECG Section 13.6.1 Adverse events of special interest	panel, specifying the method to calculate the eGFR. 3: As no ECG measurement prior to the first intake of the IMP was planned to be performed at baseline visit (V2), respective statements to document clinically significant abnormal ECG findings at baseline as medical history have been deleted. Only clinically significant abnormal ECG findings at screening (V1) have to be documented as medical history.	