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Clinical Study Protocol	
EU CT Number	2024-515907-20-00
Investigational Product	Golexanolone
Study code	UCAB-CT-05
Protocol Version and date	V 6.1; Final 03OCT2025

STUDY TITLE

A randomised, double-blind, placebo-controlled, two-part study to evaluate the pharmacokinetics, safety and tolerability, and preliminary efficacy of two dose levels of golexanolone in subjects with primary biliary cholangitis, fatigue, and cognitive dysfunction.

Test product	Golexanolone 10 mg soft gelatine capsules for oral administration
Comparator product	Placebo capsules
Sponsor signatory	PPD
Sponsor Medical Officer	PPD
Coordinating Investigator	David EJ Jones BM, BCh, FRCP, PhD OBE, Professor Freeman Hospital, Liver department, Newcastle, UK Phone: +44 0191 2137210 E-mail: david.jones@ncl.ac.uk

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The following amendments have been made to the clinical study protocol (CSP) version 1.0:

Amendment No./Response letter	**Date of Amendment/ Response letter**	**Revised CSP version** *(if applicable)*
1	20JUN2022	CSP V 2.0; 20JUN2022
Response letter MHRA	21SEP2022	CSP V 2.1; 19SEP2022 (UK specific)
2 (UK specific)	23NOV2022	CSP V 2.2; 23NOV2022 (UK specific)
Response letter BfArM	13DEC2022	CSP V 2.3; 12DEC2022 (Germany specific)
3.1 (UK specific)	26JUL2023	CSP V 3.0; 26JUL2023
3.2 (Germany specific)	26JUL2023	
3	26JUL2023	
4	16NOV2023	CSP V 4.0; 16NOV2023
5	08FEB2024	CSP V 5.0; 08FEB2024
6	05JUN2025	CSP V 6.0; 05JUN2025
6.1	03OCT2025	CSP V 6.1; 03OCT2025

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2 STUDY SYNOPSIS

Study Title

A randomised, double-blind, placebo-controlled, two-part study to evaluate the pharmacokinetics, safety and tolerability, and preliminary efficacy of two dose levels of golexanolone in subjects with primary biliary cholangitis, fatigue, and cognitive dysfunction.

Study code	**EU CT Number**
UCAB-CT-05	2024-515907-20-00
Study period Estimated date of first subject enrolled: Q3 2022 Estimated date of last subject completed : Q1 2026	**Phase of development** Phase 1b/2

Coordinating Investigator

Professor David EJ Jones BM, BCh, FRCP, PhD OBE

Professor of Liver Immunology, Newcastle University & Honorary Consultant Hepatologist, Newcastle upon Tyne Hospitals NHS Foundation Trust; Newcastle upon Tyne, UK

Background and study rationale

PBC is a chronic cholestatic liver disease characterised by progressive damage to and destruction of the small-intra-hepatic bile ducts. This leads to impairment of bile flow and progressive cholestasis leading, ultimately, to ductopenia and biliary cirrhosis. The mechanism of non-cirrhotic cognitive dysfunction in PBC remains unknown. Elevation of neurosteroid levels has been reported and related to fatigue severity. Effective treatment for central nervous system (CNS) symptoms in PBC is a key area of unmet clinical need in PBC.

Golexanolone is a synthetic epiandrosterone derivative and neurosteroid antagonist being developed for treatment of the spectrum of cognitive dysfunction associated with chronic liver disease, including that experienced by patients with PBC and hepatic encephalopathy (HE), potentially as a consequence of increased brain concentration of neurosteroids and their interactions with the gamma-aminobutyric acid (GABA)-A system. Golexanolone has the potential to reduce a major component of the GABAergic inhibitory tone without risk for seizure induction.

Golexanolone improved cognitive function and learning in two rat models of HE. Golexanolone has further been shown to antagonise the CNS effect of neurosteroids in the context of a human allopregnanolone challenge study and there are indications from a clinical study in patients with liver cirrhosis that treatment with golexanolone induces a pharmacological treatment effect on sleepiness, brain function, and cognitive function. These findings collectively suggest that golexanolone warrants further study for treatment of fatigue and cognitive impairment associate with PBC, as increased concentration of neurosteroids in the brain could be the cause of these symptoms.

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Study design

This will be a randomised, double-blind, placebo-controlled, two-part phase 1b/2 study of golexanolone versus placebo among subjects with a history of non-cirrhotic or Child-Pugh class A cirrhotic primary biliary cholangitis (PBC) with clinically significant fatigue and cognitive symptoms on stable background standard of care (SoC) PBC medication (if any). The aim of the study is to evaluate the pharmacokinetics (PK), safety and tolerability, and preliminary efficacy of golexanolone in this patient population.

The study consists of two separate parts:

A. 5 days twice daily (BID) oral administration with golexanolone 40 mg /placebo for assessment of safety and PK

B. 28 days BID oral administration with two dose levels of golexanolone/placebo for safety and preliminary efficacy

Objectives and endpoints Part A

Primary objective

To assess the safety and tolerability of treatment with 40 mg golexanolone BID for 5 days in non-cirrhotic or Child-Pugh class A cirrhotic PBC subjects with clinically significant fatigue and cognitive symptoms.

Primary endpoints

- Frequency, intensity, and seriousness of adverse events (AEs), changes from baseline to Day 5 in laboratory parameters and clinical safety parameters.

Secondary objectives

1. To assess the PK characteristics of golexanolone administered 40 mg BID for 5 days in the target population.
2. To investigate the metabolite profile of golexanolone in human plasma and urine.

Secondary endpoints

1. PK parameters:

FULL PROCEDURE:

a. after the first dose: Area under the plasma concentration time curve $(AUC)_{0\text{-}24h}$, maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), terminal elimination rate constant ($lambda_z$), terminal half-life ($T_{1/2}$), apparent volume of distribution associated with the terminal elimination phase of the plasma curve (Vz/F), total apparent clearance of drug from plasma (Cl/F).

b. after the last dose: AUC at steady state (AUC_{ss}), maximum and minimum concentration at steady state ($C_{max,\ ss}$ and $C_{min,\ ss}$), T_{max}, % fluctuation, lambdaz, $T_{1/2}$, CL/F, Vz/ F.

c. accumulation ratio between first and last dose

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MODIFIED PROCEDURE:

a. <u>after the first dose</u>: $AUC_{0\text{-}6h}$, C_{max}, T_{max}

b. <u>after the last dose</u>: AUCss, $C_{max,\ ss}$ and $C_{min,\ ss}$, T_{max}, % fluctuation, lambdaz, $T_{1/2}$, CL/F, Vz/ F

2. Metabolite profile in human plasma and urine *(to be reported separately)*.

<u>Exploratory objective</u>

To explore the inter-domain correlation across the PBC-40 domains in the target population.

Exploratory endpoint

– PBC-40 score including the domains cognition, itch, fatigue, social, emotional, and general symptoms.

Objectives and endpoints Part B

<u>Primary objective</u>

To assess the safety and tolerability of 28 days BID treatment with two dose levels of golexanolone in non-cirrhotic or Child-Pugh class A PBC subjects with clinically significant fatigue and cognitive symptoms.

Primary endpoints

1. Frequency, intensity, and seriousness of AEs, changes from baseline to Day 28 in laboratory parameters and clinical safety parameters.

<u>Secondary objectives</u>

a. To assess effects of golexanolone on health-related quality of life (HRQoL), including fatigue.

b. To assess effects of golexanolone on day-time sleepiness.

c. To assess effects of golexanolone on cognitive function.

d. To evaluate the Investigator's overall impression of treatment effect.

e. To assess the exposure of two dose levels of golexanolone in the target population treated for 28 days.

Secondary endpoints

1. Change from baseline to Day 28 in the following HRQoL measures:

   – PBC-40 scores for each of the domains (cognition, itch, fatigue, social, emotional, and general symptoms)

   – EQ-5D-3L tool

2. Change from baseline to Day 28 in daytime sleepiness related symptoms using the Epworth

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Sleepiness Scale (ESS).

3. Change from baseline to Day 28 in a battery of cognitive tests, including:
   - Portosystemic Hepatic Encephalopathy Score (PHES) total score
   - Rey Auditory Verbal Learning test (RAVLT)
   - Delis and Kaplan Executive Function System (D-KEFS) Letter and Category fluency subtests
4. Clinical Global Impression of change, PBC version (CGI-C-PBC).
5. Lowest plasma concentration before the next dose (C_{trough}) will be assessed pre-dose on Days 1, 14 and 28.

Exploratory objectives

1. To assess the plasma levels of neurosteroids and pro-inflammatory biomarkers
2. To assess effects of golexanolone on overall disease severity.

Exploratory endpoints

- Plasma concentrations of neurosteroids (*e.g.* allopregnanolone)
- Change from baseline to Day 28 in plasma concentrations of pro-inflammatory biomarkers (*e.g.* cytokines, chemokines, bile acids).
- Change from baseline to Day 28 on individual domains of the CGI-S-PBC and CGI-C-PBC (including global)

Number of subjects planned

Part A: Eight evaluable subjects will be required. Assuming a screen failure rate of 50%, it is estimated that approximately 16 subjects will be screened. Treated subjects withdrawn for other reasons than AE might be replaced, if recommended by the internal Safety Review Committee (iSRC).

Part B: Approximately 84 evaluable subjects will be required. Assuming a 10% drop-out rate, up to 93 subjects will be randomised. Assuming a screen failure rate of 50%, it is estimated that approximately 186 subjects will be screened.

When approximately 60 subjects from Part B completed Day 28 *(i.e.* 20 subjects per treatment arm), an interim analysis will be performed for sample size re-assessment. A maximum of 126 evaluable subjects may be included, dependent upon results of the re-estimation. Assuming a 10% drop-out rate, up to 139 subjects may be randomised.

Part A subjects will be allowed to enter Part B following the iSRC evaluation of Part A safety and PK data provided that data from the 6-month non-rodent toxicology study supporting >1-month treatment have been submitted to and approved by applicable Competent Authority (CA) and/or

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independent ethics committee (IEC), if requested [1]. These subjects may be screened again and randomised into one of the Part B dose groups.

Diagnosis and main eligibility criteria

Male and female subjects ≥18 years of age diagnosed with PBC, non-cirrhotic or Child-Pugh class A cirrhotic, and with presence of clinically significant fatigue and cognitive symptoms. Subjects must be on stable PBC SoC therapy (if any) for at least 3 months prior to randomisation, which may include ursodeoxycholic acid (UDCA), obeticholic acid (OCA), seladelpar, elfibranor, bezafibrate and/or fenofibrate.

Methodology

Overall description of study design

Consenting subjects will be screened for eligibility, according to study-specific inclusion/exclusion criteria within 14 days prior to the first administration of investigational medicinal product (IMP).

Study Part A

Eight eligible male and female subjects will be randomised on Day 1 (Visit 2) to 5 days of daily administration of either 40 mg BID golexanolone (6 subjects) or placebo BID (2 subjects). For subjects following the originally planned FULL PROCEDURE, PK sampling will occur frequently during the 12 hours following the first dose on Day 1, daily prior to the morning dose on Days 2 through 5, and frequently during the 48 hours following the second dose on Day 5 (evening dose). Subjects will be domiciled at the study site Days -1 to Day 7. Safety parameters will be monitored at pre-specified time-points.

An optional MODIFIED PROCEDURE involving only one overnight stay at the clinic can be chosen if the hospitalisation from Day 1 to Day 7 (included in the FULL PROCEDURE) is the only reason making the participation in Part A not possible for the subject. Subjects will come to the clinic in the morning on Day 1 for randomisation, baseline assessments and the first administration of IMP. Safety assessments and PK sampling will be performed up to 6 hours post dose, whereafter the subject leaves the clinic. The IMP will be self-administered by the subject at home from the evening dose on Day 1until the morning dose on Day 5. Study subjects will have a paper Subject Diary to record IMP intake and any new or changed concomitant medications. Study staff will call each subject daily to collect any information about AEs and remind the subject about the IMP administrations. Any AEs reported will be followed up until resolution by the site staff and if deemed necessary by the Investigator, an unscheduled visit at the clinic will be planned. Subjects will be domiciled at the study site in the afternoon on Day 5, prior to consumption of a standardised dinner and administration of the last dose of IMP, until the 12 hours post-dose PK sampling and safety assessments.

A follow-up visit will be performed on Day 21 (± 3 days), *i.e.* approximately 2 weeks after last IMP administration.

Evaluation of Part A safety and PK data

Before initiation of study Part B, an iSRC will review PK and safety data for all Part A subjects.

[1] Part A was performed in Hungary and UK only, i.e. only subjects recruited at Hungarian and UK sites may participate in both study parts.

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Exposure at 40 mg BID in part A will be evaluated in relation to the pre-defined anticipated dose levels for part B, to ensure that AUC at steady state will not supersede the pre-defined limit exposure of mean 25 000 ng/mL*h.

Based on this review, a recommendation will be made by the iSRC on whether to proceed with Part B of the study, including any adjustments of the anticipated Part B dosages judged appropriate based on the exposure results of Part A.

Study Part B

Assuming that safety and PK data from Part A are judged satisfactory by the iSRC, Part B will commence and approximately 93 subjects, assuming a 10% drop-out rate, will be randomised (1:1:1) on Day 1 (Visit 2) to administration of the anticipated dose levels of 40 mg or 80 mg golexanolone BID or placebo BID for 28 consecutive days. Adjustments of these pre-defined dose levels might be needed based on the Part A exposure. However, the maximum daily dose will not exceed 80 mg BID.

Part A subjects will be allowed to enter Part B following the iSRC evaluation of Part A safety and PK data, based on data from the 6-month non-rodent toxicology study supporting > 1-month treatment, submitted to and approved by applicable CA and/or IEC, if requested [2]. These subjects may be screened again and randomised into one of the Part B dose groups. There will be an interval of at least 1 month between last dose in Part A and first dose in Part B.

The treatment allocation (golexanolone/placebo) as well as the dose level will be double-blinded, *i.e.* it will not be disclosed to the subjects, site staff or Sponsor, except for potential un-blinding of individual subjects as described in Sections 9.1.4 and 9.1.5.

The IMP will be self-administered by the subject at home during Part B, except for the study days of visiting the clinic (Days 1, 14, and 28), when the IMP (morning dose) will be administered under supervision. A follow-up safety phone call will be performed on Day 7 and Day 21.

Intake of study medication, changes in concomitant medications and medical events occurring between visits will be registered daily by the subject in a diary. A follow-up visit will be performed on Day 42 (± 3 days), *i.e.* approximately 2 weeks after last IMP administration.

When approximately 60 subjects from Part B completed Day 28 (*i.e.* 20 subjects per treatment arm), an interim analysis will be performed for sample size re-assessment based on the effects of study drug on PBC-40 cognitive domain.

Investigational medicinal products, dosage, and mode of administration

Golexanolone will be supplied as a semi-solid lipid in soft gelatine capsules intended for oral administration. Each capsule contains 10 mg golexanolone. The excipient is a mixture of mono - and diglycerides of caprylic and capric acid, which is of pharmacopoeial quality.

Placebo capsules will contain the lipid excipient and be of identical appearance as the golexanolone capsules. The number of placebo capsules to be administered will be adjusted to match the number of golexanolone capsules administered on each dose level.

[2] Part A was performed in Hungary and UK only, i.e. only subjects recruited at Hungarian and UK sites may participate in both study parts.

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Part A: The IMP will be administered for 5 consecutive days. For subjects following the FULL PROCEDURE, all IMP will be administered at the clinic, supervised by study staff. For the MODIFIED PROCEDURE, the first dose (morning Day 1) and the last dose (evening Day 5) will be administered at the clinic. The remaining doses will be self-administered by the subject at home. The subject will be reminded daily by phone to take the IMP and the IMP intake will be registered daily in a Subject Diary. Total daily dose of golexanolone will be 80 mg (40 mg BID).

Part B: The IMP will be administered for 28 consecutive days at home by the subject. Total daily anticipated doses of golexanolone will be 80 mg and 160 mg (40 mg, and 80 mg BID).

Duration of treatment

Subjects participating in Parts A+B will receive IMP for a period of 33 days (Days 1-5 in Part A and Days 1-28 in Part B).

Subjects participating in Part A only will receive IMP for a total of 5 consecutive days. Subjects participating in Part B only will receive IMP for a total of 28 consecutive days.

To facilitate visit planning, a deviation of ±2 days for Day 28 will be acceptable.

Duration of subject's involvement in the study

Part A

Subjects will be screened for eligibility within 14 days prior to start of study treatment (Visit 1; Screening visit). Days 1-7 of the treatment period will be in-clinic (Visit 2) for subjects following the FULL PROCEDURE. The MODIFIED PROCEDURE includes only one overnight stay (Day 5 to Day 6).

A follow-up visit (Visit 3) will be performed on Day 21 (± 3 days), *i.e.* approximately 2 weeks after last IMP administration.

The total duration of subject's involvement in Part A will be maximum 5 weeks (± 3 days).

Part B

Subjects will be screened for eligibility within 14 days prior to start of study treatment (Visit 1; Screening visit).

The IMP will be self-administered at home for 28 consecutive days.

A follow-up visit will be performed on Day 42 (± 3 days), *i.e.* approximately 2 weeks after last administration of IMP.

The total duration of subject's involvement in Part B will be maximum 8 weeks (± 3 days).

Subjects participating in Parts A+B

Subjects participating in both study parts will be involved in the study for a maximum of 5 + 8 weeks with a period of at least 1 month between completion of Part A and randomisation in Part B.

Safety and tolerability assessments

- AE reporting

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- Physical examination
- Vital signs (blood pressure [BP], pulse, body temperature)
- 12-lead electrocardiogram (ECG)
- Hospital Anxiety and Depression Scale (HADS)
- Blood and urine sampling for analysis of haematology, clinical chemistry, coagulation parameters, and urinalysis

Efficacy assessments

- PBC-40 (all domains: cognition, itch, fatigue, social, emotional, and general symptoms)
- EQ-5D-3L
- ESS
- Cognitive test battery
  - PHES (5 sub-tests)
  - RAVLT
  - D-KEFS Letter and Category fluency subtests
- CGI-S-PBC, CGI-C-PBC

Pharmacokinetic assessments

Part A

Plasma samples for analysis of PK parameters will be collected before dosing and at defined time-points after first dose on Day 1 and after the evening dose on Day 5.

Plasma and urine samples will be collected for determination of golexanolone metabolite profile in human *(to be reported separately)*.

Part B

Plasma C_{trough} will be assessed pre-dose on Days 1, 14, and 28.

Exploratory assessments

- Blood sampling for analysis of plasma concentrations of neurosteroids (*e.g.* allopregnanolone) and pro-inflammatory biomarkers (*e.g.* cytokines, chemokines, bile acids).
- CGI-S-PBC, CGI-C-PBC

Ethical considerations and benefit-risk assessment

Treatment related effects observed in animal safety studies consisted of gastrointestinal disturbances (vehicle-related), increases in BP and alanine aminotransferase (ALT) elevations without concomitant histological changes.

In human studies with golexanolone there have been no safety concerns identified to this date. Golexanolone shows a favourable safety profile after single and multiple oral dosing for up to 5

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days in healthy male subjects, as well as for up to 14 and 21 days in subjects with idiopathic hypersomnia and HE, respectively. The safety risk for subjects participating in the planned study in PBC is considered acceptable based on previous experiences from subjects with liver impairment.

Previous data indicated that golexanolone decreased sleepiness, improved electroencephalography (EEG) measures and cognitive function in subjects with impaired liver function, effects that are in line with the expected action of golexanolone, *i.e.* an antagonism of neurosteroid effects in these subjects. Furthermore, golexanolone dose-dependently mitigated brain inhibitory effect of i.v. allopregnanolone. In animals, golexanolone has shown efficacy in models relevant to the mechanism of action and to the disease and is devoid of safety issues of significance for the proposed use.

The design of the study will ensure that identified risk factors are minimised whilst the scientific and medical goals for the study will be fulfilled. This taken together with the results showing neurosteroid involvement in the substantial unmet medical need in PBC subjects, the overall risk-benefit is considered favourable.

Statistical methods

General considerations

All statistical calculations will be performed using the SAS® program version 9.4 (SAS Institute Inc., Cary, NC, USA) or above. The statistical analyses will include descriptive statistics reflecting the explorative nature of the study. In general, the data will be presented by treatment arm. The data for subjects receiving placebo will be presented pooled across groups.

Continuous data, other than PK data, will be summarised by treatment arm, displaying the number of available measurements, arithmetic mean, standard deviation (SD), median, minimum, and maximum. Categorical data will be summarised by treatment arm, and as a minimum the number and percentage of subjects in each category will be presented.

Descriptive statistics for the PK parameters will be presented by dose-level with number of measurements, arithmetic mean, SD, coefficient of variation (CV), median, minimum, maximum, geometric mean, geometric CV%.

In general, P-values will be interpreted descriptively, except for the cognitive domain of PBC-40 which was chosen as the basis of sample size calculation, and where the overall type I error rate will be preserved by applying a hierarchical testing procedure.

Sample size, effect size and standard deviation

The primary objective of this study is to assess the safety and tolerability of treatment with 40 mg BID of golexanolone for 5 days (Part A) and with 40 and 80 mg BID for 28 days (Part B). With 28 subjects per treatment arm the underlying true incidence of rare Aes which didn't occur in an active treatment arm during the study does not exceed 10%, with a probability of 95%.

The main efficacy objective is to estimate the effect sizes for different secondary efficacy endpoints to enable a well-founded choice of the primary efficacy endpoint for the phase 3 confirmatory study. One of the secondary endpoints, change from baseline in the cognitive domain of PBC-40 at Day 28, was chosen as the basis of sample size estimation. An SD of 4.0 for change from baseline was assumed for all treatment arms. PBC-40 cognitive domain has a range of 6–30 score with 6 being

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normal functioning. It is assumed that an efficacious dose would have a mean (SD) decrease of 3 (4.0) points compared to placebo.

The analysis of changes from baseline in PBC-40 cognitive domain scores is planned to be performed within an analysis of covariance (ANCOVA) model accounting for treatment arm and baseline PBC-40 score as a continuous covariate. Least-square mean differences (95% confidence intervals [CIs]) between active treatment arms and placebo will be estimated within this ANCOVA framework. Although the main objective of the efficacy analysis is the estimation of effect size within the ANCOVA model, the study will be powered for the comparison between the highest dose and placebo arm.

The power is thus evaluated for the comparison of the highest dose against placebo, assuming a 3-point difference between means, and a common between-arm SD of 4.0 points. Twenty-eight evaluable subjects per treatment arm (overall N=84) will provide approximately 79.2% power for this comparison, and 82.0% power to conclude a significant overall treatment effect in the analysis of variance (ANOVA) model at a 0.05 significance level. The power estimation was performed by *proc glmpower* in SAS® version 9.4.

Interim analysis

When approximately 60 subjects from Part B completed Day 28 (*i.e.* 20 subjects per treatment arm), an interim analysis will be performed for sample size re-assessment. The originally planned overall sample size will not be decreased and no possibility for early stopping (for futility or for efficacy) is defined. The maximum overall sample size is set to 126 (a 1.5-fold increase compared to the originally planned sample size of 84).

The sample size re-estimation will be based on conditional power (CP) according to the method outlined in Chen, 2004 [1], targeting a CP of 80%. The promising zone for the CP calculated based on the observed data at the interim (CP_{obs}) ranges from 39% to 80% for this study design, therefore the sample size will be re-calculated only if CP_{obs} is contained in this range. By this procedure the overall type I error rate will be preserved.

Analysis data sets

The Intent-to-Treat (ITT) analysis set will comprise all randomised subjects.

The Modified ITT (mITT) analysis set will comprise all subjects from ITT having baseline and Day 28 measurements for at least one secondary efficacy endpoint.

The Per Protocol (PP) analysis set will comprise all subjects from mITT, with no major protocol deviations affecting efficacy.

The PK analysis set will comprise all subjects with at least one evaluable PK profile.

The Safety analysis set will comprise all subjects who received at least one dose of the IMP.

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or term	Explanation
ADL	Activities of daily living
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
ATC	Anatomic Therapeutic Chemical (classification system)
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration time curve
AUC_{ss}	AUC at steady state
BID	Twice daily *(bis in die)*
BMI	Body mass index
BP	Blood pressure
CA	Competent authority
CGI	Clinical Global Impression
CGI-C-PBC	Clinical Global Impression of change, PBC version
CGI-S-PBC	Clinical Global Impression of severity, PBC version
CI	Confidence interval
Cl/F	Total apparent clearance of drug from plasma
C_{max}	Maximum plasma concentration
$C_{max, ss}$	Maximum plasma concentration at steady state
C_{min}	Minimum plasma concentration
$C_{min, ss}$	Minimum plasma concentration at steady state
C_{trough}	Lowest plasma concentration before the next dose
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CP	Conditional power

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Abbreviation or term	Explanation
CRO	Contract research organisation
CRT	Continuous Reaction Time
CSP	Clinical study protocol
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DILI	Drug-induced liver injury
D-KEFS	Delis and Kaplan Executive Function System
DST	Digit symbol test *(a PHES sub-test)*
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EEG	Electroencephalography
ESS	Epworth Sleepiness Scale
FT3	Free triiodothyronine
FT4	Free thyroxine
GABA	Gamma-aminobutyric acid
GAMSA	GABA-A receptor modulating steroid antagonist
GCP	Good clinical practice
GDPR	General Data Protection Regulation
HADS	Hospital Anxiety and Depression Scale
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HE	Hepatic encephalopathy
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee

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Abbreviation or term	Explanation
IMP	Investigational medicinal product
INR	International Normalised Ratio
iSRC	Internal Safety Review Committee
ITT	Intent-to-Treat
IUD	Intrauterine device
$lambda_z$	Terminal elimination rate constant
LTT	Line tracing test *(a PHES sub-test)*
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
NCT-A	Number connection test-A *(a PHES sub-test)*
NCT-B	Number connection test-B *(a PHES sub-test)*
NOAEL	No observed adverse effect level
OCA	Obeticholic acid
OTC	Over the counter
PBC	Primary biliary cholangitis
PHES	Portosystemic Hepatic Encephalopathy Score
PK	Pharmacokinetics
PP	Per protocol
PT	Preferred term
PV	Pharmacovigilance
RAVLT	Rey Auditory Verbal Learning test
SAR	Serious adverse reaction
SAE	Serious adverse event
SD	Standard deviation
SDT	Serial dotting test *(a PHES sub-test)*
SDV	Source data verification
SoC	Standard of care
SOC	System organ class

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Abbreviation or term	**Explanation**
SOP	Standard operating procedure
SRC	Safety Review Committee
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	Terminal half-life
TEAE	Treatment emergent AE
T_{max}	Time to C_{max}
TSH	Thyroid-stimulating hormone
UDCA	Ursodeoxycholic acid
ULN	Upper limit of normal
Vz/F	Apparent volume of distribution associated with the terminal elimination phase of the plasma curve
WOCBP	Women of childbearing potential
Enrolled subject	Subject who has signed the ICF
Screen failure	Enrolled subject not included
Included subject	Subject randomised
Withdrawn subject	Subject randomised but not completed
Completed subject	Subject completed the study period, including follow-up

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5 ETHICAL AND REGULATORY REQUIREMENTS

5.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki [2] and are consistent with International Council for Harmonisation (ICH)/Good Clinical Practice (GCP) E6 (R2), EU Regulation (Eu) No 536/2014, and applicable local regulatory requirements.

5.2 Ethics and regulatory review

The clinical study protocol (CSP), the subject information and informed consent form (ICF), any other written information to be provided to the subjects and any advertisements used for recruitment of subjects will be submitted to applicable independent ethics committee (IEC) for approval.

Study documents will be submitted to the applicable competent authority (CA) for approval according to local regulatory requirements.

Approval must be obtained from both IEC and CA before the first subject can be recruited.

The Sponsor will provide the CA, IEC, and Principal Investigators with safety updates/reports according to local requirements. Progress reports and notifications of Suspected unexpected serious adverse reactions (SUSARs) will be provided to the IEC according to local regulations and guidelines.

5.3 Subject information and consent

It is the responsibility of the Investigator or an authorised associate to give each potential study subject adequate verbal and written information regarding the objectives and the procedures of the study as well as any risks or inconvenience involved before any study specific assessments are performed. The subject must be informed that participation in the study is voluntary and that the subject may withdraw from participation at any time and for any reason, without any prejudice. The subject will be given the opportunity to ask questions about the study and will be allowed sufficient time for consideration of the proposal.

Before performing any study-related procedures the ICF must be signed and personally dated by the subject and by the Investigator. A copy of the subject information including the signed ICF will be provided to the subject.

Documentation of the discussion and the date of informed consent must be recorded in the source documentation and in the electronic case report form (eCRF). The subject information sheet and the signed ICF must be filed by the Investigator for possible future audits and/or inspections.

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The final approved version of the subject information and ICF must not be changed without approval from the Sponsor and the applicable IEC.

The subject information and the ICF must be revised whenever there are changes to the study procedures or when new information becomes available that might affect the willingness of the subject to participate. Subjects must be re-consented to the most current version of the ICF (or to significant new information addendum) in accordance with applicable laws and IEC policy during their participation in the study.

5.4 Subject card

The subject will be provided with a subject card including the following information:

- Subject study ID
- That he/she is participating in this clinical study
- That he/she will be/has been treated with the investigational medicinal product (IMP)
- Dosing instructions
- The name and phone number of the Investigator
- Name and address of the Sponsor
- Information about disallowed concomitant medications

5.5 Subject data protection

The potential study subject will be informed that the study data will be recorded, collected, and processed and may be transferred to European Economic Area (EEA) or non-EEA countries. In accordance with the European General Data Protection Regulation (GDPR) (EU) 2016/679 and the UK Data Protection, Privacy and Electronic Communication, the data will not identify any persons taking part in the study.

The potential study subject should be informed that by signing the ICF he/she approves that authorised representatives from the Sponsor and Accelsiors, the IEC and the CA have direct access to his/her medical records for verification of clinical study procedures.

The subject has the right to request access to his/her personal data and the right to request rectification of any data that is not correct and/or complete in accordance with applicable local regulations. The request will be raised to the Principal Investigator.

The Investigator must file a *Subject Identification List* which includes sufficient information to link records, *i.e.* the eCRF and clinical records. This list should be preserved for possible future inspections/audits but should not be made available to the Sponsor or Accelsiors, except for monitoring or auditing purposes.

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Personal data that are collected in the study such as health information and ethnicity are considered as sensitive personal data. This data will be pseudonymised, *i.e.* personally identifiable information will be removed and replaced by a unique subject ID and will be processed by the Sponsor and other involved parties during the study. After the study end, only pseudonymised data, *i.e.* aggregated data sets, can be used.

For this study, the Sponsor is the data controller of all data processed during the study (*e.g.* Study Master File, clinical study report) and Accelsiors, is the data processor. Any subcontractors used in the study, are also data processors. For data that are processed at the clinic (*e.g.* medical records and Investigator site file), the clinic is the data controller.

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6 INVESTIGATOR(S) AND STUDY ADMINISTRATIVE STRUCTURE

Sponsor

Umecrine Cognition AB
Nanna Svartz väg 6A
SE-171 65 Solna, Sweden

Sponsor Signatory

PPD

Sponsor Medical Officer

PPD

Clinical Project Managers

PPD

PPD

Clinical Research Organisation (project management, data management, biostatistics, SUSAR reporting and clinical monitoring)

Accelsiors CRO
Haros st. 103
1222 Budapest, Hungary

Project Manager

PPD

Statistician

PPD

Data Manager

PPD

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Study sites

Coordinating site Freeman Hospital Liver department Newcastle Tyne and Wear NE7 7DN, UK	**Coordinating Investigator** David EJ Jones BM, BCh, FRCP, PhD OBE, Professor Phone: +44 0191 2137210 E-mail: david.jones@ncl.ac.uk
Part A study sites *These sites will participate also in Part B* Facility of CRU Hungary Ltd. Pest Megyei Flór Ferenc Kórház Kistarcsa 2143 Semmelweis tér 1,Hungary	**Principal Investigator** Géza Lakner, MD Phone: +36 703966690 E-mail: lakner.geza@hungarnet.hu
Clinexpert Ltd. Phase I Clinical Trial Site Bugát Pál Hospital Dózsa György u. 15-17 3200 Gyöngyös, Hungary	**Principal Investigator** István Láng, MD, PhD, Professor Phone: +36 309505314 E-mail: prof.lang.istvan@clinexpert.hu
Nottingham University Hospitals NHS Trust Queen's Medical Centre Derby Road, Nottingham, NG7 2UH UK	**Principal Investigator** Stephen Ryder, MD, PhD, Professor Phone:+44 (0)115 924 9924 E-mail: Stephen.Ryder@nuh.nhs.uk
NIHR Birmingham BRC ITM Building, Mindelsohn Way University of Birmingham Birmingham, B15 2TT, UK	**Principal Investigator** Palak Trivedi, MD, PhD, Professor Phone: +44 (0)1213718173 E-mail: p.j.trivedi@bham.ac.uk

In Part B of the study, additional countries and sites will be included.

Central laboratory for safety laboratory analyses GBA Central Lab Services GmbH (former LKF-Laboratorium für Klinische Forschung GmbH) Lise-Meitner-Strasse 25-29 24223 Schwentinental, Germany	**Contact person** Bärbel Wilke Phone: +49 4307 8276 0 E-mail: project-cls@gba-group.com

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Pharmacokinetic bioanalyses Lablytica Life Science AB Virdings Allee 16 754 50 Uppsala, Sweden	**Contact persons** PPD PPD
Pharmacokinetic calculations CTC Clinical Trial Consultants AB Dag Hammarskjölds väg 10B SE-752 37 Uppsala, Sweden	**Senior pharmacokineticist** PPD
Metabolite screening MetaSafe AB Forskargatan 20J 151 36 Södertälje, Sweden	**Contact person** PPD
Analysis of neurosteroids and pro-inflammatory biomarkers Admescope Ltd Typpitie 1 90620 Oulu, Finland	**Contact person** PPD
Manufacturing, packaging, labelling and release of bulk IMP	CCI
Primary and clinical packaging, labelling, storage, QP release and distribution of subject-specific IMP kits to non-EU sites	CCI
QP release, labelling, storage and distribution of subject-specific IMP kits to EU sites	CCI

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QP release, labelling, storage, and distribution of subject-specific IMP kits	CCI [redacted]

Signatures required are provided in Appendix 13.1.

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7 INTRODUCTION

A summary of information about the active IMP (golexanolone) is given in this section. More detailed information can be found in the Investigator's Brochure [3].

7.1 Primary biliary cholangitis

Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease characterised by progressive damage to and destruction of the small-intra-hepatic bile ducts. This leads to impairment of bile flow and progressive cholestasis leading, ultimately, to ductopenia and biliary cirrhosis.

Primary biliary cholangitis patients at all disease stages can experience significant cognitive symptoms [4, 5, 6, 7]. These symptoms are not a consequence of hepatic encephalopathy (HE), as most affected patients are not cirrhotic, and conventional HE is uncommon in PBC. Central fatigue is the most common symptom and affects ~60% of patients, approximately half of whom experience a markedly reduced quality of life. Standardised testing indicates that cognitive dysfunction, characterised by patients as "brain fog" with difficulty in concentrating and processing information and impaired short-term memory [8] is next most common symptom. Fatigue and cognitive dysfunction also overlap in a significant subset of patients.

The mechanism of non-cirrhotic cognitive dysfunction in PBC remains unknown. Elevation of neurosteroid levels has been reported and related to fatigue severity [9]. Effective treatment for central nervous system (CNS) symptoms in PBC is a key area of unmet clinical need in PBC [10].

7.2 Investigational medicinal product

Golexanolone (internal code GR3027) is a synthetic epiandrosterone derivative and neurosteroid antagonist being developed for treatment of the spectrum of cognitive dysfunction associated with chronic liver disease, including that experienced by patients with PBC and HE, potentially as a consequence of increased brain concentration of neurosteroids and their interactions with the gamma-aminobutyric acid (GABA)-A system. Golexanolone has the potential to reduce a major component of the GABAergic inhibitory tone without risk for seizure induction.

Golexanolone improved cognitive function and learning in two rat models of HE [11]. The nonclinical safety profile of the compound has been documented as appropriate for clinical use of up to 6 months duration.

The ability of oral golexanolone to enter the CNS, engage its target and exert a pharmacodynamic effect was demonstrated in healthy adult males in the first-in-human (FIH) study UCAB-CT-01 using allopregnanolone challenge and 3 and 30 mg of golexanolone as

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single doses [12]. The results indicated that oral golexanolone dose-dependently mitigated the inhibitory effects of allopregnanolone on brain function as measured by sleepiness and saccadic eye velocity.

Preliminary evidence of golexanolone benefit on cognitive function was demonstrated in cirrhotic patients with Child-Pugh class A/B cirrhosis and evidence of covert HE in clinical study UCAB-CT-02 [13]. Part D of this randomised, double-blind, placebo-controlled study indicated that 21 days of twice daily (BID) golexanolone dosing was associated with improvements in cognitive function, brain function and sleepiness as measured by Continuous Reaction Time (CRT), electroencephalography (EEG) and Epworth Sleepiness Scale (ESS).

Golexanolone has exhibited excellent tolerability and linear pharmacokinetics (PK) in healthy subjects during single ascending dose (SAD) [12] and multiple ascending dose (MAD) [13] at doses far above those which mitigate the brain-inhibitory effects of i.v. allopregnanolone [12].

Similarly, in patients with Child-Pugh class A/B cirrhosis, safety, and tolerability of single and multiple dose golexanolone administration was satisfactory at doses which appear to improve cognition in subjects with covert HE [13]. The analysis of dose-proportionality in these liver impaired patients showed a tendency to higher exposure with dose, with modest accumulation at higher doses.

Collectively, the studies indicate that golexanolone shows satisfactory safety and tolerability, exhibits the expected pharmacodynamic effect in healthy adults and shows early evidence of clinical benefit in subjects with cirrhosis and HE at the same doses proposed for this study.

7.3 Study rationale

Allopregnanolone and isopregnanolone are increased in the plasma of patients with chronic fatigue syndrome [14], and in patients with PBC or chronic hepatitis C with evidence of fatigue as measured by the fatigue impact scale. Such increase is not seen among PBC or chronic hepatitis C patients without evidence of fatigue [9]. Very recently, circulating levels of allopregnanolone have been shown to be elevated in PBC patients with evidence of cognitive dysfunction based on PBC-40 but not in PBC controls [15]. The present preliminary findings therefore suggest that increased inhibition through GABA-A receptors due to the accumulation of neuroinhibitory steroids may represent an important pathophysiological mechanism of fatigue and cognitive dysfunction in chronic liver diseases. Collectively, these findings strongly implicate allosteric activation of GABA-A receptors/GABA-ergic transmission as mediators of the cognitive dysfunction manifested clinically as HE among patients with cirrhosis as well as in the fatigue and cognitive impairment experienced by patients with PBC.

Golexanolone has further been shown to antagonise the CNS effect of neurosteroids in the context of a human allopregnanolone challenge study [12] and there are indications from the

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extended treatment part of the UCAB-CT-02 study in patients with liver cirrhosis that treatment with golexanolone induces a pharmacological treatment effect on sleepiness, brain function, and cognitive function. These findings collectively suggest that golexanolone warrants further study for treatment of fatigue and cognitive impairment associate with PBC, as increased concentration of neurosteroids in the brain could be the cause of these symptoms.

7.4 Risk/benefit assessment

7.4.1 Unmet medical need

Primary biliary cholangitis is only slowly progressive, and the majority of patients do not progress to cirrhosis, dying “with” the disease rather than “from” it.

The CNS manifestations such as cognitive symptoms and fatigue are problematic for PBC patients, especially those whose occupations or activities of daily living require information processing. These symptoms do not improve with currently licensed therapies (ursodeoxycholic acid [UDCA] and obeticholic acid [OCA]) [16, 17, 18] and ongoing studies of anti-cholestatic therapy are looking unpromising. Effective treatment for CNS symptoms in PBC is a key area of unmet clinical need [10,19].

7.4.2 Risk assessment

Treatment related effects observed in animal safety studies consisted of gastrointestinal disturbances (vehicle-related), increases in blood pressure (BP) and alanine aminotransferase (ALT) elevations without concomitant histological changes.

In human studies with golexanolone there have been no safety concerns identified to this date. Golexanolone shows a favourable safety profile after single and multiple oral dosing for up to 5 days in healthy male subjects, as well as for up to 14 and 21 days in subjects with idiopathic hypersomnia and HE, respectively. The safety risk for subjects participating in the planned study in PBC is considered acceptable based on previous experiences from subjects with liver impairment.

Previous data indicated that golexanolone decreased sleepiness, improved EEG measures and cognitive function in subjects with impaired liver function, effects that are in line with the expected action of golexanolone, *i.e.* an antagonism of neurosteroid effects in these subjects. Furthermore, golexanolone dose-dependently mitigated brain inhibitory effect of i.v. allopregnanolone. In animals, golexanolone has shown efficacy in models relevant to the mechanism of action and to the disease and is devoid of safety issues of significance for the proposed use.

This taken together with the results showing neurosteroid involvement in the substantial unmet medical need of PBC patients, the overall risk-benefit is considered favourable.

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7.4.3 Summary of risk management

In the first part of the study (Part A) it will be optional for study subjects to remain at the study site from the evening before first dosing (Day -1) until 2 days following the last dose of IMP (Day 7) or to follow an out-patient MODIFIED PROCEDURE with self-administration at home and only one overnight stay. During the confinement to the clinic all subjects will be closely monitored by medical staff. For subjects following the MODIFIED PROCEDURE, site staff will call the subject daily during the out-patient period (from Day 1 evening to Day 5 morning) to collect information on any adverse events (AEs), changes in concomitant medications and compliance with IMP intake. Any AEs reported will be followed up until resolution by the site staff and if deemed necessary by the Investigator, an unscheduled visit at the clinic will be planned. In addition, to further assure treatment compliance, the subjects will note IMP intake and concomitant medications in a Subject Diary.

Before initiation of study Part B an internal Safety Review Committee (iSRC) will review PK and safety data for all Part A subjects. Based on this review, a recommendation will be made on whether to proceed with Part B of the study, including any adjustments in Part B dosage judged appropriate based on the exposure results of Part A.

Part A subjects will be allowed to enter Part B, based on data from the 6-month non-rodent toxicology study supporting >1-month treatment. A Safety Review Committee (SRC) will be established to oversee the safe conduct of study Part B.

Risks and discomfort related to medical devices used in the study (*e.g.* indwelling venous catheters and BP and electrocardiogram (ECG) measuring devices) are considered low and ethically justifiable since these devices are used in routine medical care.

The anticipated volume of blood samples collected during the study from a subject participating in both study parts will not exceed 460 mL (*i.e.* the volume drawn during a regular blood donation).

Current recommendations from the authorities with regards to the coronavirus disease 2019 (COVID-19) pandemic will be considered on a day-to-day basis. Assessment sessions with Sponsors, Investigators, and contract research organisation (CRO)/vendor representative members to align on local restrictions, impact assessment, contingency plans and study-specific risk mitigation strategies will be made to safeguard the study conduct and the safety of the subjects included in the study. Risks regarding subject safety, study performance and data quality/integrity will hence be assessed on an ongoing basis during the study.

Altogether, the design of the study will ensure that the aforementioned risk factors are minimised whilst the scientific and medical goals for the study will be fulfilled.

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8 STUDY OBJECTIVES AND ENDPOINTS

8.1 Primary objectives and endpoints

Objectives	Endpoints	Assessments
Primary, Part A		
To assess the safety and tolerability of treatment with 40 mg golexanolone BID for 5 days in non-cirrhotic or Child-Pugh class A cirrhotic PBC subjects with clinically significant fatigue and cognitive symptoms.	Frequency, intensity, and seriousness of Aes, changes from baseline to Day 5 in laboratory parameters and clinical safety parameters	– Physical examination (see Section 9.5.3.1) – Vital signs (see Section 9.5.3.2) – 12-lead ECG (see Section 9.5.3.3) – Hospital Anxiety and Depression Scale (HADS) [20, 21] (see Section 9.5.3.4). – Safety laboratory parameters (see Section 9.5.4) – AE reporting (see Section 9.5.5)
Primary, Part B		
To assess the safety and tolerability of 28 days BID treatment with two dose levels of golexanolone in non-cirrhotic or Child-Pugh class A PBC subjects with clinically significant fatigue and cognitive symptoms.	Frequency, intensity, and seriousness of Aes, changes from baseline to Day 28 in laboratory parameters and clinical safety parameters	– Physical examination (see Section 9.5.3.1) – Vital signs (see Section 9.5.3.2) – 12-lead ECG (see Section 9.5.3.3) – HADS (see Section 9.5.3.4).

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Objectives	Endpoints	Assessments
		– Safety laboratory parameters (see Section 9.5.4) – AE reporting (see Section 9.5.5)

8.2 Secondary objectives and endpoints

Objectives	Endpoints	Assessments
Secondary, Part A		
1. To assess the PK characteristics of golexanolone administered 40 mg BID for 5 days in the target population.	PK parameters: FULL PROCEDURE: a. after the first dose: area under the plasma concentration time curve (AUC) $_{0\text{-}24h}$, maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), terminal elimination rate constant ($lambda_z$), terminal half-life ($T_{1/2}$), apparent volume of distribution associated with the terminal elimination phase of the plasma curve (Vz/F), total apparent clearance of drug from plasma (Cl/F) b. after the last dose: AUC at steady state (AUCss), C_{max} and C_{min} at steady state	– PK sampling (see Section 9.5.6)

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Objectives	Endpoints	Assessments
	($C_{max, ss}$ and $C_{min, ss}$), T_{max}, % fluctuation, lambdaz, $T_{1/2}$, CL/F, Vz/ F c. accumulation ratio between first and last dose MODIFIED PROCEDURE: a. after the first dose: AUC_{0-6h}, C_{max}, T_{max} b. after the last dose: AUCss, $C_{max, ss}$ and $C_{min, ss}$, T_{max}, % fluctuation, lambdaz, $T_{1/2}$, CL/F, Vz/ F	
2. To investigate the metabolite profile of golexanolone in human plasma and urine.	Metabolite profile in human plasma and urine (to be reported separately)	– PK sampling (see Section 9.5.6)
Secondary, Part B		
1. To assess effects of golexanolone on health-related quality of life (HRQoL), including fatigue.	Change from baseline to Day 28 in the following HRQoL measures: – PBC-40 scores for each of the domains (cognition, itch, fatigue, social, emotional, and general symptoms) – EQ-5D-3L tool	– PBC-40 questionnaire (see Section 9.5.7.1) – EQ-5D-3L questionnaire (see Section 9.5.7.2)

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Objectives	Endpoints	Assessments
2. To assess effects of golexanolone on day-time sleepiness.	Change from baseline to Day 28 in daytime sleepiness related symptoms using the ESS [22]	– ESS questionnaire (see Section 9.5.7.3)
3. To assess effects of golexanolone on cognitive function.	Change from baseline to Day 28 in a battery of cognitive tests, including: – Portosystemic Hepatic Encephalopathy Score (PHES) total score [23, 24, 25] – Rey Auditory Verbal Learning test (RAVLT) [26]	– PHES assessment (see Section 9.5.7.4) – RAVLT assessment (see Section 9.5.7.5)
	– Delis and Kaplan Executive Function System (D-KEFS) Letter and Category fluency subtests [27]	– D-KEFS assessment (see Section 9.5.7.6)
4. To evaluate the Investigator's overall impression of treatment effect.	Clinical Global Impression of change, PBC version (CGI-C-PBC)	– CGI-S-PBC and CGI-C-PBC assessment (see Section 9.5.7.7)
5. To assess the exposure of two dose levels of golexanolone in the target population treated for 28 days.	The lowest plasma concentration before the next dose (C_{trough}) will be assessed pre-dose on Days 1, 14, and 28	– PK sampling (see Section 9.5.6)

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8.3 Exploratory objectives and endpoints

Objectives	Endpoints	Assessments
Exploratory, Part A		
To explore the inter-domain correlation across the PBC-40 domains in the target population.	– PBC-40 score including the domains cognition, itch, fatigue, social, emotional, and general symptoms [5]	– PBC-40 questionnaire (see Section 9.5.7.1)
Exploratory, Part B		
1. To assess the plasma levels of neurosteroids and pro-inflammatory biomarkers	– Plasma concentrations of neurosteroids (*e.g.* allopregnanolone) – Change from baseline to Day 28 in plasma concentrations of pro-inflammatory biomarkers (*e.g.* cytokines, chemokines, bile acids)	– Sampling for neurosteroids (*e.g.* allopregnanolone and pro-inflammatory biomarkers (*e.g.* cytokines, chemokines, bile acids) (see Section 9.5.8.1)
2. To assess effects of golexanolone on overall disease severity.	– Change from baseline to Day 28 on individual domains of the CGI-S-PBC and CGI-C-PBC (including global)	– CGI-S-PBC and CGI-C-PBC assessment (see Section 9.5.7.7)

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9 INVESTIGATIONAL PLAN

9.1 Overall study design and schedule of events

This will be a randomised, double-blind, placebo-controlled, two-part phase 1b/2 study of golexanolone among subjects with a history of non-cirrhotic or Child-Pugh class A cirrhotic PBC with clinically significant fatigue and cognitive symptoms and on stable background standard of care (SoC) PBC medication (if any). The aim of the study is to evaluate the PK, safety and tolerability, and preliminary efficacy of golexanolone in this patient population.

The study consists of two separate parts:

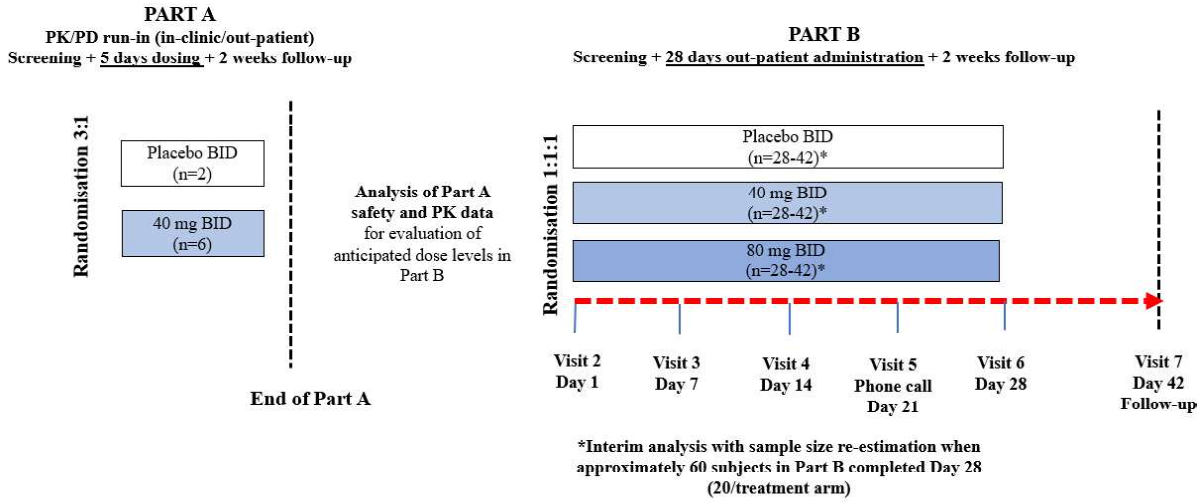
A. 5 days BID oral administration with golexanolone 40 mg /placebo for assessment of safety and PK

B. 28 days BID oral administration with two dose levels of golexanolone/placebo for safety and preliminary efficacy

Consenting subjects will be screened for eligibility, according to study-specific inclusion/exclusion criteria within 14 days prior to the first administration of IMP.

A flow-chart of the overall study design is presented in Figure 9.1-1.

Figure 9.1-1 Flow-chart, overall study design



9.1.1 Study Part A

Eight eligible male and female subjects will be randomised on Day 1 (Visit 2) to 5 days of daily administration of either 40 mg BID golexanolone (6 subjects) or placebo BID (2 subjects). For subjects following the originally planned FULL PROCEDURE, PK

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sampling will occur frequently during the 12 hours following the first dose on Day 1, daily prior to the morning dose on Days 2 through 5, and frequently during the 48 hours following the second dose on Day 5 (evening dose). Subjects will be domiciled at the study site Days -1 to Day 7. Safety parameters will be monitored at pre-specified time-points.

An optional MODIFIED PROCEDURE involving only one overnight stay at the clinic can be chosen if the hospitalisation from Day 1 to Day 7 (included in the FULL PROCEDURE) is the only reason making the participation in Part A not possible for the subject. Subjects will come to the clinic in the morning on Day 1 for randomisation, baseline assessments and the first administration of IMP. Safety assessments and PK sampling will be performed up to 6 hours post dose, whereafter the subject leaves the clinic. The IMP will be self-administered by the subject at home from the evening dose on Day 1until the morning dose on Day 5. Study subjects will have a paper Subject Diary to record IMP intake and any new or changed concomitant medications. Study staff will call each subject daily to collect any information about AEs and remind the subject about the IMP administrations. Any AEs reported will be followed up until resolution by the site staff and if deemed necessary by the Investigator, an unscheduled visit at the clinic will be planned. Subjects will be domiciled at the study site in the afternoon on Day 5, prior to consumption of a standardised dinner and administration of the last dose of IMP, until the 12 hours post-dose PK sampling and safety assessments.

A follow-up visit (Visit 3) will be performed on Day 21 (± 3 days), *i.e.* approximately 2 weeks after last IMP administration.

Visits and assessments in Part A FULL PROCEDURE will be performed as described in Table 9.1-1 to Table 9.1-4. Visits and assessments in Part A, MODIFIED PROCEDURE will be performed as described in Table 9.1-5 to Table 9.1-7.

Each assessment is further described in Section 9.5.

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Table 9.1-1 Overall schedule of events Part A; ***FULL PROCEDURE***

	Visit 1 screening	Visit 2 In-clinic								Visit 3 Follow-up
Assessments **Day**	**-14 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**21±3**
Informed consent	X									
Demographics	X									
Medical/surgical history	X									
Inclusion/exclusion criteria	X	X[1]	X[1]							
Weight, height[2], BMI	X	X								X
Physical examination	X							X		X
Vital signs (BP and pulse)	X	X	X	X	X	X	X	X	X	X
Vital signs (body temperature)	X	X	X		X	X	X	X		X
ECG	X		X	X	X	X	X	X		
HADS	X		X					X		
HIV, Hepatitis B and C	X									
Haematology, clinical chemistry, coagulation	X		X	X[3]		X[3]		X		X
Urine analysis (dip stick)	X	X						X		X
Pregnancy test	X[4]	X[5, 6]								X[5]
Alcohol breath test	X	X								X
FSH and oestradiol	X[7]									
Randomisation			X							
IMP administration			X	X	X	X	X			
PK blood sampling			X	X	X	X	X	X	X	
- Aliquot for metabolite profile							X	X	X	
Urine for metabolite profile							X[8]			
PBC-40	X		X					X		
AE reporting (including SAEs)	X	X	X[9]							
TEAE reporting (including SAEs)			X[10]	X	X	X	X	X	X	X
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X

1. Confirmation of relevant inclusion/exclusion criteria
2. Height only at screening
3. Limited panel (see Section 9.5.4)
4. Serum pregnancy test, WOCBP only
5. Urine dipstick pregnancy test, WOCBP only
6. Can be performed on Day -1 OR on Day 1 prior to first administration of IMP
7. In questionable cases to confirm post-menopausal state
8. Urine collection pre-dose, 0-2, 2-4, 4-8, 8-12 h
9. Until first administration of IMP
10. From first administration of IMP

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Table 9.1-2 Detailed schedule of events Part A, Days 1-2; ***FULL PROCEDURE***

	In-clinic period (Visit 2)														
Day	**Day 1**													**Day 2**	
Time/ assessments	**Pre-dose**	**0**	**20'**	**40'**	**60'**	**90'**	**120'**	**180'**	**4h**	**6h**	**8h**	**9h**	**12h**	**24h**	**36h**
Inclusion/exclusion criteria	X[1]														
Vital signs (BP and pulse)	X		X		X		X	X	X	X		X	X	X	
Vital signs (body temperature)	X												X		
ECG	X				X		X							X	
HADS	X														
Haematology, clinical chemistry, coagulation	X[2]													X[3]	
Pregnancy test	X[4]														
Randomisation	X														
IMP administration		X											X	X	X
Blood sampling for PK	X[6]		X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]		X[5]	X[5,6]	X[5,6]	X[5,6]
PBC-40	X														
AE reporting (including SAEs)	X[7]														
TEAE reporting (including SAEs)		X[8]													
Prior and concomitant medications	X														

1. Confirmation of relevant inclusion/exclusion criteria
2. Full panel (see Section 9.5.4)
3. Limited panel (see Section 9.5.4)
4. Urine dipstick pregnancy test, WOCBP only. Can be performed on Day -1 OR on Day 1 pre-dose
5. PK sampling to be performed as close as possible to the scheduled time (± 10% up to the 24-hour post-dose time-point, thereafter ±3 hours)
6. Within 10 min pre-dose
7. Until first administration of IMP
8. From first administration of IMP

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Table 9.1-3 Detailed schedule of events Part A, Days 3-4; ***FULL PROCEDURE***

Day	**In-clinic period Days 3 and 4**											
Time/ assessments	**Pre-dose**	**0**	**20'**	**60'**	**90'**	**120'**	**180'**	**4h**	**6h**	**8h**	**9h**	**12h**
Vital signs (BP and pulse)	X		X	X		X	X	X	X		X	X
Vital signs (body temperature)	X											X
ECG	X			X		X						
Haematology, clinical chemistry, coagulation	X[1]											
IMP administration		X										X
PK blood sampling	X[2,]											X[2, 3]
TEAE reporting (including SAEs)	X											
Concomitant medications	X											

1. Day 4 only. Limited panel (see Section 9.5.4)
2. Within 10 min pre-dose
3. PK sampling to be performed as close as possible to the scheduled time (± 10% up to the 24-hour post-dose time-point, thereafter ±3 hours)

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Table 9.1-4 Detailed schedule of events Part A, Days 5-7; ***FULL PROCEDURE***

	In-clinic period (Visit 2)																								
Day	**Day 5**																					**Day 6**			**D 7**
Time/ assessments	**Pre-dose**	**0**	**20'**	**60'**	**90'**	**120'**	**180'**	**4h**	**6h**	**8h**	**9h**	**12h**	**12h 20'**	**12h 40'**	**13h**	**13h 30'**	**14h**	**15h**	**16h**	**18h**	**21h**	**24h**	**30h**	**36h**	**60h**
Physical examination																						X			
Vital signs (BP and pulse)	X		X	X		X	X	X	X		X	X										X			X
Vital signs (body temperature)	X											X										X			
ECG	X			X		X																X			
HADS																						X			
Haematology, clinical chemistry, coagulation																						X[1]			
Urine analysis (dip stick)																						X			
IMP administration		X										X													
Blood sampling for PK	X[2,3]											X[2,3]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
-Aliquot for metabolite profile	X[2,3]											X[2,3]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Urine for metabolite profile	X	X[4]																							
PBC-40																						X			
TEAE reporting (incl. SAEs)	X																								
Concomitant medications	X																								

1. Full panel (see Section 9.5.4)
2. PK sampling to be performed as close as possible to the scheduled time (± 10% up to the 24-hour post-dose time-point, thereafter ±3 hours)
3. Within 10 min pre-dose
4. Urine collection 0-2, 2-4, 4-8, 8-12 h

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Table 9.1-5 Overall schedule of events Part A; ***MODIFIED PROCEDURE***

		Visit 1 screening	Visit 2						Visit 3
			Clinic visit	Self-administration at home			Over-night stay		Follow-up
Assessments	**Day**	**-14 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**21±3**
Informed consent		X							
Demographics		X							
Medical/surgical history		X							
Inclusion/exclusion criteria		X	X[1]						
Weight, height[2], BMI		X	X						X
Physical examination		X						X	X
Vital signs (BP and pulse)		X	X				X	X	X
Vital signs (body temperature)		X	X				X	X	X
ECG		X	X				X	X	
HADS		X	X					X	
HIV, Hepatitis B and C		X							
Haematology, clinical chemistry, coagulation		X	X					X	X
Urine analysis (dip stick)		X	X					X	X
Pregnancy test		X[3]	X[4]						X
Alcohol breath test		X	X				X		X
FSH and oestradiol		X[5]							
Randomisation			X						
IMP administration[6]			X	X	X	X	X		
IMP dispensing			X						
IMP accountability							X		
Diary instructions and dispensing			X						
Phone reminders				X	X	X	X		
Subject diary completion			X	X	X	X	X		
Subject diary review							X		
PK blood sampling			X				X	X	
- Aliquot for metabolite profile							X	X	
Urine for metabolite profile							X[7]	X[7]	
PBC-40		X	X					X	
AE reporting (including SAEs)		X	X[8]						
TEAE reporting (including SAEs)			X[9]	X	X	X	X	X	X
Prior and concomitant medications		X	X	X	X	X	X	X	X

1. Confirmation of relevant inclusion/exclusion criteria
2. Height only at screening
3. Serum pregnancy test, WOCBP only
4. Urine dipstick pregnancy test, WOCBP only
5. In questionable cases to confirm post-menopausal state
6. Day 1 morning and Day 5 evening at the clinic, remaining doses at home
7. Urine collection pre-dose, 0-2, 2-4, 4-8, 8-12 h post last dose
8. Until first administration of IMP
9. From first administration of IMP

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Table 9.1-6 Detailed schedule of events Part A, Day 1; ***MODIFIED PROCEDURE***

Day	**Day 1**									
Time/ assessments	**Pre-dose**	**0**	**20'**	**40'**	**60'**	**90'**	**120'**	**180'**	**4h**	**6h**
Inclusion/exclusion criteria	X[1]									
Weight, BMI	X									
Vital signs (BP and pulse)	X		X		X		X	X	X	X
Vital signs (body temperature)	X									X
ECG	X				X		X			X
HADS	X									
Haematology, clinical chemistry, coagulation	X[2]									X[3]
Urine analysis (dip stick)	X									
Pregnancy test	X[4]									
Alcohol breath test	X									
Randomisation	X									
IMP administration		X[5]								
IMP dispensing										X
Diary instructions and dispensing										X
Blood sampling for PK	X[6]		X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]
PBC-40	X									
AE reporting (including SAEs)	X[8]									
TEAE reporting (including SAEs)		X[9]								
Prior and concomitant medications	X									

1. Confirmation of relevant inclusion/exclusion criteria
2. Full panel (see Section 9.5.4)
3. Limited panel (see Section 9.5.4)
4. Urine dipstick pregnancy test, WOCBP only
5. IMP administration at the clinic
6. Within 10 min pre-dose
7. PK sampling to be performed as close as possible to the scheduled time (± 10%)
8. Until first administration of IMP
9. From first administration of IMP

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Table 9.1-7 Detailed schedule of events Part A, Days 5-6; ***MODIFIED PROCEDURE***

Day	**Day 5**													**Day 6**
Time/ assessments	**Pre Dose 9**	**0**	**Pre Dose 10**	**12h**	**12h 20'**	**12h 40'**	**13h**	**13h 30'**	**14h**	**15h**	**16h**	**18h**	**21h**	**24h**
Phone reminder	X													
IMP administration		X[1]		X[2]										
IMP accountability			X											
Subject diary completion		X												
Confinement to clinic			X[3]											
Subject diary review			X											
Physical examination														X
Vital signs (BP and pulse)			X											X
Vital signs (body temperature)			X											X
ECG			X											X
HADS														X
Haematology, clinical chemistry, coagulation														X[4]
Urine analysis (dip stick)														X
Pregnancy test			X[5]											
Alcohol breath test			X											
Blood sampling for PK			X[7]		X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]
-Aliquot for metabolite profile			X[7]		X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]
Urine for metabolite profile			X	X[8]										
PBC-40														X
TEAE reporting (incl. SAEs)	X													

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Day	**Day 5**												**Day 6**
Time/ assessments	**Pre Dose 9**	**0**	**Pre Dose 10**	**12h**	**12h 20'**	**12h 40'**	**13h**	**13h 30'**	**14h**	**15h**	**16h**	**18h**	**21h**	**24h**
Concomitant medications	X													

1. IMP administration at home
2. IMP administration at the clinic
3. A standardised dinner will be served at the clinic 3 hours before the last dose
4. Full panel (see Section 9.5.4)
5. Urine dipstick pregnancy test, WOCBP only
6. PK sampling to be performed as close as possible to the scheduled time (± 10%)
7. Within 10 min pre-dose
8. Urine collection 0-2, 2-4, 4-8, 8-12 h post last dose

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9.1.2 Evaluation of Part A safety and pharmacokinetic data

Before initiation of study Part B, the iSRC will review PK and safety data for all Part A subjects. Exposure at 40 mg BID in part A will be evaluated in relation to the pre-defined dose levels for part B, to ensure that AUC at steady state will not supersede the pre-defined limit exposure (see Section 9.2.2).

Based on this review, a recommendation will be made by the iSRC on whether to proceed with Part B of the study, including any adjustments of the anticipated Part B dosage judged appropriate based on the exposure results of Part A.

9.1.3 Study Part B

Assuming that safety and PK data from Part A are judged satisfactory by the iSRC, Part B will commence and approximately 93 subjects, assuming a 10% drop-out rate, will be randomised (1:1:1) on Day 1 (Visit 2) to administration of the anticipated dose levels of 40 mg or 80 mg golexanolone BID or placebo BID for 28 consecutive days. Adjustments of these pre-defined dose levels might be needed based on the Part A exposure. However, the maximum daily dose is not to exceed 80 mg BID.

Part A subjects will be allowed to enter Part B following the iSRC evaluation of Part A safety and PK data, based on data from the 6-month non-rodent toxicology study supporting >1-month treatment, submitted to and approved by applicable CA and/or IEC, if requested [3]. These subjects may be screened again and randomised into one of the Part B dose groups. There will be an interval of at least 1 month between last dose in Part A and first dose in Part B.

The treatment allocation (golexanolone/placebo) as well as the dose level will be double-blinded, *i.e.* it will not be disclosed to the subjects, site staff or Sponsor, except for potential un-blinding of individual subjects as described in Sections 9.1.4 and 9.1.5.

The IMP will be self-administered by the subject at home during Part B, except for the study days of visiting the clinic (Days 1, 14, and 28), when the IMP (morning dose) will be administered under supervision. A follow-up safety phone call will be performed on Day 7 and Day 21.

Intake of study medication, changes in concomitant medications and medical events occurring between visits will be registered daily by the subject in a diary. A follow-up visit will be performed on Day 42 (± 3 days), *i.e.* approximately 2 weeks after last IMP administration.

[3] Part A was performed in Hungary and UK only, i.e. only subjects recruited at Hungarian and UK sites may participate in both study parts.

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When approximately 60 subjects from Part B completed Day 28 (*i.e.* 20 subjects per treatment arm) an interim analysis will be performed for sample size re-assessment based on the effects of study drug on PBC-40 cognitive domain (see Section 9.8.2).

Visits and assessments in Part B will be performed as described in Table 9.1-8. Each assessment is further described in Section 9.5.

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Table 9.1-8 Schedule of events Part B

		Visit 1 Screening	Visit 2 Baseline Randomisation	Visit 3 Phone review	Visit 4	Visit 5 Phone review	Visit 6	Visit 7 Follow-up
Assessments	**Day**	**-14 to -1**	**1**	**7 ±2**	**14 ±2**	**21 ±2**	**28 ±2**	**42 ±3**
Informed consent		X						
Demographics		X						
Medical/surgical history		X						
Inclusion/exclusion criteria		X	X[1]					
Weight, height[2], BMI		X	X					X
Physical examination		X			X			X
Vital signs (BP and pulse)		X	X		X		X	X
Vital signs (body temperature)		X	X		X			X
ECG		X	X		X		X	
HADS			X		X		X	
HIV, Hepatitis B and C		X						
Haematology, clinical chemistry, coagulation		X	X		X		X	X
Urine analysis (dip stick)		X	X				X	X
Pregnancy test		X[3]	X[4]					X[4]
Alcohol breath test		X	X		X		X	X
FSH and oestradiol		X[5]						
Randomisation			X					
Dispensing of IMP			X		X			
IMP accountability[6]					X		X	

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		Visit 1 Screening	Visit 2 Baseline Randomisation	Visit 3 Phone review	Visit 4	Visit 5 Phone review	Visit 6	Visit 7 Follow-up
Assessments	**Day**	**-14 to -1**	**1**	**7 ±2**	**14 ±2**	**21 ±2**	**28 ±2**	**42 ±3**
PK blood sampling			X[7]		X[7]		X[7]	
Blood sampling for neurosteroids and pro-inflammatory biomarkers			X				X	
PBC-40		X	X		X		X	
ESS, EQ-5D-3L			X		X		X	
Practice session for cognitive tests (PHES, RAVLT, D-		X[8]						
Cognitive tests (PHES, RAVLT, D-KEFS)			X[9]		X		X[9]	
CGI-S-PBC			X[10]				X	
CGI-C-PBC							X	
AE reporting (including SAEs)		X	X[11]					
TEAE reporting (including SAEs)			X[12]	X	X	X	X	X
Prior and concomitant medications		X	X	X	X	X	X	X

1. Pre-dose, confirmation of relevant inclusion/exclusion criteria
2. Height only at screening
3. Serum pregnancy test, WOCBP only
4. Urine dipstick pregnancy test, WOCBP only
5. In questionable cases to confirm post-menopausal state
6. Accountability of unused capsules and used wallets returned by the subject
7. Pre-dose
8. For purposes of familiarising subjects with cognitive tests
9. For D-KEFS where alternate forms of tests are used (*i.e.* word lists, fluency tasks) the form used at visit 2 (Baseline) should be same as form used at Visit 6 (28 days, end of treatment).
10. Interview to confirm baseline status to be considered for the CGI assessment at end of treatment
11. Until administration of IMP
12. From administration of IMP

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9.1.4 Internal Safety Review Committee

An iSRC will be established to oversee the safe conduct of study Part A. The iSRC will consist of:

- The Coordinating Investigator
- A Sponsor medical representative
- The Medical Monitor at Accelsiors

The pharmacokineticist will be un-blinded and will not participate in the decisions of the iSRC. Further internal or external experts may be consulted by the iSRC as necessary.

The randomisation code for individual subjects may be broken by the iSRC during the assessment process (partial un-blinding). In case of partial un-blinding, the Coordinating Investigator will not have access to un-blinded data for subjects recruited at his own site. All other parties would remain blinded.

The iSRC responsibilities will include review of aggregate PK and safety data from Part A and based on this review recommend whether to proceed with Part B of the study including any adjustments of the anticipated Part B dosage judged appropriate based on the exposure results of Part A.

A study-specific iSRC charter will describe the composition of and procedures to be followed by the iSRC. The recommendations of the iSRC will be agreed in consensus between the iSRC members and documented as specified in the iSRC charter.

9.1.5 Safety Review Committee

A SRC, including at least one individual with no involvement in the study, will be established to oversee the safe conduct of study Part B. The SRC will meet regularly to oversee the safe conduct of the study, including the safety perspective of the interim analysis and recommendations on sample size re-estimation.

The randomisation code may be broken for individual subjects by the SRC during the assessment process (partial un-blinding). In case of partial un-blinding, the Coordinating Investigator will not have access to un-blinded data for subjects recruited at his own site.. All other parties would remain blinded.

A study specific SRC charter will describe the composition of and procedures to be followed by the SRC. The recommendations of the SRC will be agreed in consensus between the SRC members and documented as specified in the SRC charter.

In case of a recommendation to suspend or terminate the study, the SRC will be required to provide the rationale for its recommendation. In the unlikely case where the Sponsor decides not to follow the recommendation of the SRC, the Sponsor will need to provide an appropriate justification for such decision. In such case, the rationale for SRC recommendation and Sponsor’s justification for the decision not to follow SRC recommendation may need to be

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submitted to competent authorities and ethics committees, depending on local reporting requirements.

9.2 Rationale for study design, doses, and control group

9.2.1 Study design

Both study parts (A and B) will be placebo-controlled and randomised. In order to minimise potential bias or placebo effect, all study personal, including Sponsor, CRO and Investigators will be blinded, except for potential un-blinding of individual subjects as described in Sections 9.1.4 and 9.1.5.

There is currently no approved treatment for fatigue and/or cognitive dysfunction in subjects with PBC, therefore golexanolone is being compared with placebo in this study. Stable treatment with SoC PBC medications will be allowed during the study. Therefore, apart from prohibited medications, subjects participating in the study will not be denied access to any PBC therapy which has been prescribed by their treating physician, as long as it can be maintained stable during study participation.

The treatment duration of 28 days in part B is considered sufficient to reach steady state (achieved after 5 days of dosing in previous clinical studies), evaluate the safety profile of golexanolone in subjects with PBC and to generate preliminary efficacy data. In the clinical study in subjects with liver cirrhosis and manifestations of cognitive impairment (UCAB-CT-02) 21 days treatment with golexanolone induced a pharmacological treatment effect on sleepiness, brain function, and cognitive function [13].

Before initiation of study Part B, exposure at 40 mg BID in part A will be evaluated in relation to the pre-defined anticipated dose levels for part B, based on AUC and the pre-defined limit exposure (see Section 9.2.2).

The cut-offs for clinically significant fatigue (PBC-40 fatigue domain score of ≥29) and cognitive symptoms (PBC-40 cognitive domain ≥16) used for inclusion have been defined based on a publication by Newton et. al. [28].

The use of hormonal contraceptives will not be allowed during the study, other than intrauterine hormone-releasing system (IUS), transdermal (*e.g.* patches, gels and sprays) or local (*e.g.* vaginal tablets, gels, creams, rings, suppositories) administration of oestrogen or progesterone, which are allowed. Golexanolone is a steroid derivative that inhibits allosteric activation of GABA-A receptors by endogenous allopregnanolone. Since progesterone or synthetic progestins in hormonal contraceptives are metabolised to allopregnanolone or allopregnanolone-like molecules, it is possible that hormonal contraceptives, by generating allopregnanolone, might interfere with study interpretation. Moreover, *in vitro* studies suggest that golexanolone may be an inducer of in particular intestinal CYP3A4 and thereby diminish the effectiveness of oral contraceptives (see Investigator's Brochure Section 5.2.8) [3]. Early embryonic and embryofoetal development studies or drug-drug interaction studies

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with golexanolone have not yet been performed. Therefore, because both ethinylestradiol and progesterone/progestins are CYP3A4 substrates, they are disallowed in this study.

9.2.1.1 Justification for Part A MODIFIED PROCEDURE

An optional Part A MODIFIED PROCEDURE involving only one overnight stay at the clinic has been introduced in an amendment to the CSP to mitigate the recruitment difficulties encountered and facilitate completion of Part A in a reasonable time. The MODIFIED PROCEDURE includes PK sampling and safety assessments up to 6 hours post dose on Day 1 and an overnight stay at the clinic between Days 5 and 6. PK sampling and safety assessments will be performed until 12 hours post last dose of IMP. The IMP will be self-administered by the subject at home from the evening dose on Day 1 until the morning dose on Day 5. The modifications made are considered not to jeopardise the scientific value of the study or to have any safety risks to study subjects as justified below.

Pharmacokinetic considerations

The MODIFIED PROCEDURE will not provide a full PK profile on Day 1. However, the same PK data will be obtained when the plasma concentrations are the highest. AUC_{0-6} will be captured as well as C_{max}, based on previous data. The main comparison with cirrhotic patients (40 mg dose cohort in study UCAB-CT-02) will be based on AUC_{ss} at Day 5 (see Section 9.2.2) following the last dose. Plasma samples will be collected for up to 12 hours at the same timepoints as for the FULL PROCEDURE. The AUC_{ss} 0-12 hours will give the AUC under a dosing interval and is the AUC that will be compared to the AUC in cirrhotic patients. The data for the subjects following the FULL PROCEDURE will be amalgamated with the data from the subjects following the MODIFIED PROCEDURE. This will give sufficient information to compare the PK in PBC subjects with previous clinical experience and to justify the dose selection for part B.

To assure that the study subjects are taking the IMP as instructed during the self-administration period (evening Day 1 to Morning Day 5), intake of the IMP and any new or changed concomitant medications will be recorded by the subject in a paper Subject Diary. Study staff will call each subject daily to collect any information about AEs and remind the subject about the IMP administration.

Safety considerations

Golexanolone has demonstrated an excellent safety profile in prior preclinical models and clinical studies, inclusive but not limited to patients with advanced hepatic impairment. Overall, treatment with golexanolone at doses up to 80 mg BID for 21 consecutive days was generally well tolerated in subjects with liver cirrhosis. No safety concerns were identified in the clinical studies performed with golexanolone (please see Investigator's Brochure Section 6.4) [3].

In the current study, a total of 8 subjects will be evaluated in Part A (6 treated with active IMP, 2 treated with placebo). Until this date, 3 subjects (at least 1 subject with active IMP)

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with PBC have been treated with 40 mg BID for 5 days and have completed Part A. The dose given can be compared to the treatment regimen of 80 mg golexanolone for 21 days given in previous studies with patients with liver cirrhosis. No safety concerns have been identified so far.

The Part A MODIFIED PROCEDURE will limit the time at the hospital site to 6 hours after first dose at Day 1 and 12 hours after the last dose at Day 5, compared to confinement from Day 1 to Day 7 in the FULL PROCEDURE. Consequently, the number of safety assessments will be reduced, including monitoring of any AEs by hospital staff. However, sufficient information of the wellbeing and safety (AEs) of the study subjects will be collected through daily telephone calls and follow-up as needed. Any AEs reported will be followed up until resolution by the site staff and if deemed necessary by the Investigator, an unscheduled visit at the clinic will be planned.

Given that the population under investigation in the current study is not in more advanced disease state than previous liver cirrhosis population and will be exposed to half the maximum dose, 40 mg BID compared to 80 mg BID, the planned regular safety evaluation over the phone for the 6-day duration of Part A MODIFIED PROCEDURE does not render any unacceptable risk for subjects' wellbeing.

9.2.2 Dose selection

For this study, two dose levels of golexanolone (40 mg BID and 80 mg BID) have been selected. The dose selection is based on prior human data and non-clinical safety.

Dose-limiting organ toxicity has not been observed at the maximum feasible dose in any of the investigated species (rats, dogs and minipigs). In the minipig CNS-related clinical signs were observed at the highest dose tested. At NOAEL exposure was about 15 (C_{max}) to 20-fold (AUC) higher than that observed at 80 mg BID in patients in study UCAB-CT-02 (See Investigator's Brochure Section 5.3.6).

In Part C of study UCAB-CT-02, 24 subjects with C-P A/B cirrhosis received placebo or golexanolone or 10 mg BID, 40 mg BID, and 80 mg BID for 5 consecutive days [13]. Safety was judged satisfactory and steady state was reached in all dose groups.

In Part D of study UCAB-CT-02, a total of 33 male and female subjects with C-P A/B cirrhosis were dosed for up to 21 days (30 subjects completed) with 10 mg BID, 40 mg BID or 80 mg BID of golexanolone. Safety was judged satisfactory. The results indicated that employed doses of golexanolone induces a pharmacological treatment effect on sleepiness, brain function, and cognitive function. Based on results in animal models of cognition, the predicted exposures at the suggested dose levels are expected to be pharmacologically efficacious.

Golexanolone administration in subjects with PBC and/or cholestatic-predominant liver disease has not been studied and it cannot be ruled out that an impaired biliary excretion in these subjects might influence the elimination. Therefore, protocol UCAB-CT-05 includes a

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run-in Part A which will randomise 8 subjects with non-cirrhotic or C-P class A PBC to 5 days of dosing with golexanolone 40 mg BID or placebo BID (6:2).

A starting dose of 40 mg BID in Part A is anticipated to be safe and expected to give a more relevant estimate of the potential effect of a decreased biliary excretion in comparison to a lower dose. The 40 mg dose will enable a direct comparison of PK between subjects with PBC and the previously studied subjects with cirrhosis. Subjects following the FULL PROCEDURE will be domiciled at the study site Days 1-7 for continuous surveillance. Subjects following the MODIFIED PROCEDURE will be observed at the clinic until 6 hours following the first dose on Day 1 and until 12 hours following the last dose on Day 5.

The proposed dosing is consistent with the approach in liver impaired subjects recommended in the report by Verbeeck [29], which indicates that the bioavailability of drugs with a moderate to high hepatic extraction ratio may be increased two-fold and sometimes more.

Before initiation of Part B, the iSRC will review PK and safety data for all Part A subjects. Part B will be initiated based on data from the 6-month chronic toxicity study in minipigs are available. Assuming satisfactory safety and PK, and if recommended by the iSRC, the randomised, double-blind placebo-controlled study Part B will be initiated consisting of parallel enrolment into the pre-planned dose groups 40 mg BID, 80 mg BID, and placebo. Depending on the exposure levels achieved in Part A, dose levels in Part B may be adjusted to mimic the expected exposure levels from the pre-planned dose groups.

The systemic exposure (AUC_{ss} Day 5) in study Part A (40 mg) will be compared to a previously conducted patient cohort with 40 mg golexanolone (Study UCAB-CT-02). If the geometric mean value for AUC_{ss} Day 5 from Part A is within 80 – 120% of what previously has been observed (3463 h*ng/mL, see Investigator's Brochure Table 6.2-2), no dose adjustments for Part B will be considered due to PK reasons. Should the exposure in Part A fall outside of the 80-120% range, the low dose level in Part B might be adjusted to target 3463 h*ng/mL, assuming linear PK and when considering the availability of capsule dosage strengths. The high dose level in Part B will be twice as high as the low dose level and will never exceed 80 mg. Thus, the dose levels can only be adjusted downwards. The iSRC will make the final judgement whether a potential dose adjustment is needed after reviewing Part A safety and PK data.

9.3 Selection of study population

9.3.1 Recruitment

Subjects will be recruited from the participating clinics and from a network of referring clinics, as applicable.

Part A subjects will be recruited from a limited number of sites in Hungary and UK only.

Recruitment will be competitive among sites in both study parts.

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9.3.2 Number of subjects

Part A: Eight evaluable subjects will be required. Assuming a screen failure rate of 50%, it is estimated that approximately 16 subjects will be screened. Treated subjects withdrawn for other reasons than AE might be replaced, if recommended by the iSRC.

Part B: Approximately 84 evaluable subjects will be required. Assuming a 10% drop-out rate, up to 93 subjects will be randomised. Assuming a screen failure rate of 50%, it is estimated that approximately 186 subjects will be screened.

When approximately 60 subjects from Part B completed Day 28 (*i.e.* 20 subjects per treatment arm), an interim analysis will be performed for sample size re-assessment. A maximum of 126 evaluable subjects may be included, dependent upon results of the re-estimation. Assuming a 10% drop-out rate, up to 139 subjects will be randomised.

Part A subjects will be allowed to enter Part B following the iSRC evaluation of Part A safety and PK data provided that data from the 6-month non-rodent toxicology study supporting > 1 month's treatment have been submitted to and approved by applicable CA and/or IEC, if requested [4]. These subjects may be screened again and randomised into one of the Part B dose groups.

9.3.3 Screening and enrolment log

The Investigator will keep a log of all subjects screened and included. The reason for screen failure should be stated for all subjects screened but not included. The reason for withdrawal should be stated for all subjects included but not completed.

Subjects who have signed the ICF will be assigned a unique Subject ID which will be used for unique identification of the subject. Subjects randomised will be assigned a unique randomisation number.

9.3.4 Screening failures

Screening failures are defined as subjects who consent to participate in the clinical study but do not fulfil all eligibility criteria and are not subsequently included in the study. A minimal set of screening failure information is required to ensure transparent reporting of screening failure subjects. Minimal information includes documentation of signed and dated ICF and reason(s) for screen failure.

[4] Part A will be performed in Hungary and UK only, i.e. only subjects recruited at Hungarian and UK sites may participate in both study parts.

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Re-screening can be performed once/subject if any of the following was the reason for screening failure or non-inclusion (as judged by the Investigator):

- Practical reasons (*e.g.* inability to schedule the randomisation visit within given timeframe)
- Non-significant medical conditions (*e.g.* COVID-19, influenza, nasopharyngitis)

Subjects screened and considered as fulfilling all eligibility criteria but not randomised due to the temporary halt for non-safety reasons will be allowed to be re-screened even if previously re-screened once for the reasons given above.

If an assessment needs to be re-evaluated after the 14 days screening period, for the same reasons as given above, the subject will be considered as re-screened.

For subjects who are re-screened, a new Subject ID will be assigned and a new, signed ICF will be collected.

If a subject failed due to a laboratory value or other parameter that, in this patient population, can be expected to fluctuate over time, the assessment can be re-evaluated once within the 14 days screening period. This will not be considered a re-screening, only as a repeated assessment.

9.3.5 Inclusion criteria

For inclusion in the study subjects must fulfil all the following criteria:

1. Male and female subjects age ≥ 18 years.
2. Diagnosis of PBC based on the presence of ≥2 of the 3 key disease characteristics:
    a. Anti-mitochondrial antibody or PBC-specific anti-nuclear antibody titre ≥1/40
    b. Elevated alkaline phosphatase (ALP) (> upper limit of normal [ULN] for the relevant laboratory)
    c. Compatible or diagnostic liver biopsy
3. Clinically significant fatigue defined for the purposes of this study as a PBC-40 fatigue domain score of ≥29 at screening.
4. Clinically significant cognitive symptoms, defined for the purposes of this study as a PBC-40 cognitive domain ≥16 at screening.
5. Stable PBC SoC therapy (if any), which may include UDCA, OCA, seladelpar, elfibranor, bezafibrate and/or fenofibrate for at least 3 months prior to randomisation.
6. For all women of childbearing potential (WOCBP) a negative pregnancy test at screening and a negative urine dip-stick pregnancy test at baseline, prior to first dose of IMP will be required.

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7. WOCBP must be willing to use a contraceptive method with a failure rate of < 1% (intrauterine device [IUD], intrauterine hormone-releasing system [IUS], transdermal or local hormonal contraception, bilateral tubal occlusion, vasectomised partner, sexual abstinence), and agree to continue use of this method for the duration of the study and thereafter for 1 month after the last dosing of the IMP. Note that IUS, transdermal (*e.g.* patches, gels and sprays) or local (*e.g.* vaginal tablets, gels, creams, rings, suppositories) administration of oestrogen or progesterone are the only hormonal contraceptive methods allowed due to possible interactions with the IMP.
8. Females of non-childbearing potential must have documented tubal ligation or hysterectomy; or be post-menopausal (defined as 12 months of amenorrhoea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) 25-140 IE/L and oestradiol <200 pmol/L is confirmatory]).
9. Fertile male subjects must be willing to use condom and assure that their female partner will use contraceptive methods with a failure rate of < 1%[5] to prevent pregnancy and drug exposure of a fertile female partner and refrain from donating sperm from the date of dosing until 1 month after dosing of the IMP. Men who are surgically sterile may be included without they/their partner fulfilling the above criteria on birth control.
10. Willing and able to give informed consent.
11. The subject should be judged by the Investigator to be lucid and oriented to person, place, time, and situation when giving the informed consent.

9.3.6 Exclusion criteria

Subjects must not be included in the study if any of the following exclusion criteria are fulfilled:

1. Child-Pugh class B or C cirrhosis.
2. Clinical evidence of hepatic decompensation (*e.g.* current or prior HE, ascites, or variceal bleeding).
3. History of hepatocellular carcinoma.
4. Bilirubin >1.5 x ULN.
5. Glomerular filtration rate (GFR) <35 mL/min/1.73m^2 estimated using the CKD-EPI equation.

[5] Combined (oestrogen 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), IUD, IUS, bilateral tubal occlusion, vasectomy, sexual abstinence.

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6. Haemoglobin (HB) <110 g/L, *i.e.* subjects with moderate/severe anaemia.
7. S-B12 < 125 pmol/L or P-folate < 7 nmol/L.
8. Evidence of biliary obstruction.
9. Any positive result on screening for human immunodeficiency virus (HIV), or hepatitis B (serum hepatitis B surface antigen positive). Subjects positive for HCV antibodies should be tested for PCR HCV RNA and in case of positive result considered as not eligible.
10. Prolonged QTcF (>500 ms), or any clinically significant abnormality in the resting ECG, as judged by the Investigator (at screening).
11. Concomitant disease characterised by chronic fatigue and/or cognitive impairment (*e.g.* Alzheimer's, Parkinson's, etc.) which in the judgement of the Investigator would either limit the potential benefit to the subject and/or confound the interpretation of results.
12. Clinically significant bowel disease, including obstruction, active inflammatory bowel disease, or malabsorption.
13. Clinically significant sleep apnoea, as defined by >5 episodes/hour more than 70% of occasions, despite use of continuous positive airway pressure (CPAP).
14. An uncontrolled thyroid disorder:
    a. Uncontrolled hyperthyroidism: defined as any history of hyperthyroidism that has either not been treated with either radioactive iodine and/or surgery or that has been treated with radioactive iodine and/or surgery but has required ongoing continuous or intermittent use of thyroid hormone synthesis inhibitors (*i.e.* methimazole or propylthiouracil) in the 24 weeks before screening.
    b. Uncontrolled hypothyroidism: defined as initiation of thyroid hormone replacement therapy or dose adjustment of replacement therapy in the 12 weeks before screening.
    c. Subjects without a diagnosed thyroid disease should be excluded if thyroid-stimulating hormone (TSH)-value is above ULN, or/and if free triiodothyronine (FT3)- or free thyroxine (FT4)-values are outside normal limits.
15. Subjects with a history of or currently active immune disorders (*i.e.* uncontrolled) other that PBC (including autoimmune disease) and/or diseases requiring immunosuppressive drugs (including azathioprine, prednisone, prednisolone, oral budesonide, cyclosporine, tacrolimus, methotrexate, or mycophenolate mofetil).
16. Clinical diagnosis of autoimmune hepatitis overlap defined using the Paris overlap criteria (see Appendix 13.2) [30, 31].
17. *Criterion deleted but numbering unchanged.*

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18. The presence, as judged by the Investigator, of clinically significant concomitant illness which would jeopardise safe participation in the study and /or the interpretation of study findings, *e.g.* major psychiatric disorder, such as major depressive disorder formally diagnosed by a psychiatrist.
19. Regular use of prescribed or over the counter (OTC) medications that in the opinion of the Investigator are causing fatigue or cognitive dysfunction to the subject. Examples include benzodiazepines, sedating antihistamines (first generation), anticonvulsants, sedating antidepressants (*e.g.* tricyclic and sedating heterocyclic antidepressants), anticholinergics (benztropine), antiparkinsonian medications (amantadine, selegiline, benztropine), psychostimulants, narcotic medications within 4 weeks prior to baseline. The purpose is to assure that any change observed in cognition can be associated with study drug and not any concomitant medication.
20. Use of prohibited medications within 14 days prior to randomisation, as specified in Section 9.4.8.2.
21. Anticipated change in PBC medication and/or significant medical or surgical intervention within the duration of the study.
22. Regular (more than 1 week per month) alcohol consumption in excess of 14 units per week.
23. Administration of another new chemical entity (defined as a compound that has not been approved for marketing) or has participated in any other clinical study that included drug treatment with the last administration within 3 months prior to administration of IMP in this study.
24. Females who are pregnant, nursing or actively trying to conceive a child.
25. Expected inability to swallow the required number of IMP capsules at the applicable dose level.
26. History of severe allergy/hypersensitivity or on-going allergy/hypersensitivity, as judged by the Investigator. Known allergy or hypersensitivity to drugs with a similar chemical structure or class to golexanolone, *i.e.* GABAA receptor modulating steroid antagonists (GAMSA). Known allergy of or hypersensitivity to any other component of the investigational drug (*i.e.* glyceryl mono and dicaprylocaprate).
27. Investigator considers the subject unlikely to comply with study procedures, restrictions, and requirements.

9.3.7 Restrictions

The following restrictions must be respected by the subjects participating in the study Part A; FULL PROCEDURE:

- Fasting: The subjects should be fasting overnight (8 hours) before Day 1. A standardised dinner will be served 3 hours before the second daily dose on Day 5.

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- Alcohol: Consumption of alcohol is not allowed 24 hours prior to and during all clinic visits.
- Coffee: Consumption of up to five cups of coffee (or other caffeine-containing beverage) per day will be allowed during the in-clinic-period (*i.e.* from confinement on Day -1 until Day 7).
- Xanthine or taurine containing products/beverages: Energy drinks (*e.g.* Redbull or similar) are not allowed during the in-clinic-period (*i.e.* from confinement on Day -1 until Day 7).
- Grapefruit and grapefruit containing products, or products containing peel of grapefruit or oranges (*e.g.* Seville oranges) are not allowed during the in-clinic-period (*i.e.* from confinement on Day -1 until Day 7).
- Participation in other clinical studies: The subjects are not allowed to participate in any other interventional clinical study during the study period.

The following restrictions must be respected by the subjects participating in the study Part A; MODIFIED PROCEDURE:

- Fasting: The subjects should be fasting overnight (8 hours) before Day 1. Subjects should be instructed not to eat within 2 hours from the planned time for IMP administration in the evening on Day 5.
- Alcohol: Consumption of alcohol is not allowed 24 hours prior to all clinic visits and during the treatment and PK sampling period (*i.e.* from Day 1 until discharge at Day 6).
- Coffee: Consumption of up to five cups of coffee (or other caffeine-containing beverage) per day will be allowed during the treatment and PK sampling period (*i.e.* from Day 1 until discharge at Day 6).
- Xanthine or taurine containing products/beverages: Energy drinks (*e.g.* Redbull or similar) are not allowed during the treatment and PK sampling period (*i.e.* from Day 1 until discharge at Day 6).
- Grapefruit and grapefruit containing products, or products containing peel of grapefruit or oranges (*e.g.* Seville oranges) are not allowed during the treatment and PK sampling period (*i.e.* from Day 1 until discharge at Day 6).
- Participation in other clinical studies: The subjects are not allowed to participate in any other interventional clinical study during the study period.

The following restrictions must be respected by the subjects participating in the study Part B:

- Fasting: The subjects should be fasting overnight (8 hours) before the visits to the clinic on Days 1, 14, and 28.

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- Alcohol: Consumption of alcohol is not allowed within 24 hours prior to and during all clinic visits.
- Consumption of coffee and xanthene containing drinks (including coffee, caffeine containing tea, red bull etc.) should follow the subject's normal daily pattern of consumption.
- Participation in other clinical studies: The subjects are not allowed to participate in any other interventional clinical study during the study period.

Restrictions related to concomitant therapy are described in Section 9.4.8.

9.3.8 Contraception requirements

All WOCBP must practice effective contraception during the study and be willing and able to continue contraception for at least 1 month after their last dose of IMP. Effective contraception is defined as use of a contraceptive method with a failure rate of < 1% (IUD, IUS, transdermal or local hormonal contraception, bilateral tubal occlusion, vasectomised partner, sexual abstinence), and agree to continue use of this method for the duration of the study and thereafter for 1 month after the last dosing of the IMP. Note that IUS, transdermal (*e.g.* patches, gels and sprays) or local (*e.g.* vaginal tablets, gels, creams, rings, suppositories) administration of oestrogen or progesterone are the only hormonal contraceptive methods allowed due to possible interactions with the IMP. Women who are surgically sterile or post-menopausal (defined as 12 months of amenorrhoea [in questionable cases a blood sample with simultaneous FSH 25-140 IE/L and oestradiol <200 pmol/L is confirmatory]) may be included without fulfilling the above criteria on birth control.

Fertile male subjects must be willing to use condom and assure that their female partner will use contraceptive methods with a failure rate of < 1% to prevent pregnancy and drug exposure of a fertile female partner and refrain from donating sperm from the date of dosing until 1 month after dosing of the IMP. Contraceptive methods with a failure rate of < 1% are:

- Combined (oestrogen 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)
- IUD
- IUS
- Bilateral tubal occlusion
- Vasectomy
- Sexual abstinence

Men who are surgically sterile may be included without they/their partner fulfilling the above criteria on birth control.

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Abstinence can be considered an acceptable method of contraception if it is the preferred and usual lifestyle of the subject, at the discretion of the Investigator. Abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. Periodic abstinence (*e.g.* calendar, ovulation, symptom-thermal, post-ovulation methods) and withdrawal are not considered acceptable methods of contraception.

9.3.9 Removal of subjects from therapy or assessment

9.3.9.1 General withdrawal criteria

Subjects are free to discontinue their participation in the study at any time and for whatever reason without affecting their right to an appropriate follow-up investigation or their future care. If possible, the reason for withdrawal of consent should be documented.

Subjects may be discontinued from the study at any time at the discretion of the Investigator for any of the following reasons:

- Severe non-compliance to CSP procedures, as judged by the Investigator and/or Sponsor
- Subject is lost to follow-up

Subjects must be discontinued from the study at any time for any of the following reasons:

- Significant AEs posing a risk for the subject
- Pregnancy or suspicion of possible pregnancy

Irrespective of the reason for withdrawal and whenever possible, the subject should be examined. Relevant laboratory test samples should be obtained, and all relevant assessments should be completed, preferably according to the scheme for the final assessment. Any ongoing AEs will be followed as described in Section 9.5.5.9.

The primary reason for discontinuation/early withdrawal must be specified in the eCRF and final drug accountability must be performed.

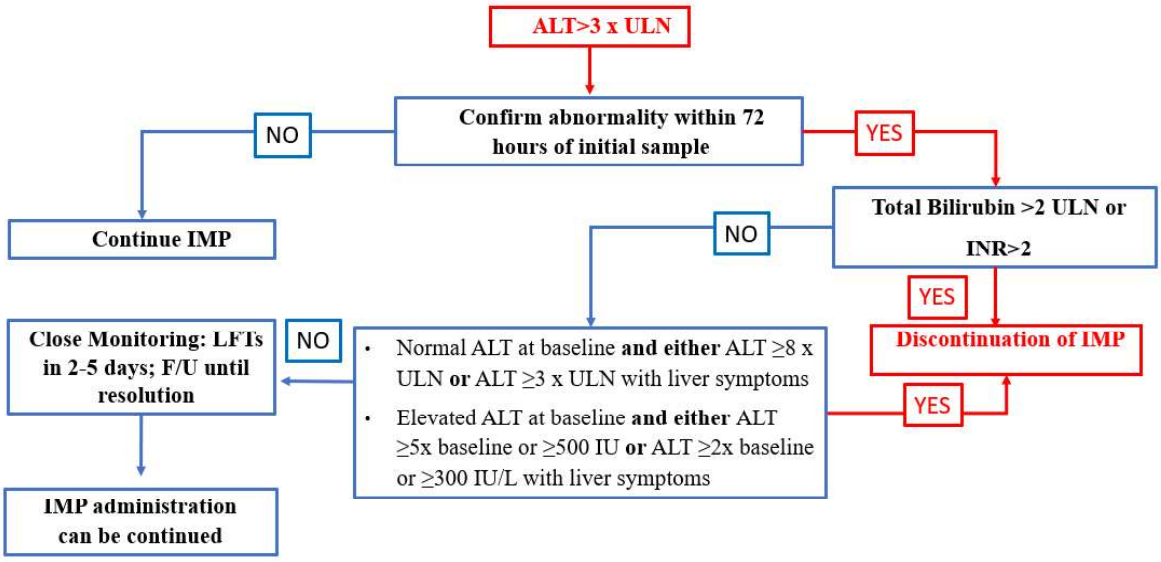
Generally, a withdrawn subject is not allowed to re-enter into the study. However, subjects withdrawn for administrative reasons, *e.g.* due to the temporary halt for non-safety reasons, are allowed to be randomised again.

9.3.9.2 Individual treatment stopping criteria

Subjects must undergo accelerated liver biochemical safety monitoring to assess the possibility of drug-induced liver injury (DILI) if significant abnormalities are detected during the study as depicted in Figure 9.3-1. This includes repeat of AST, ALT, ALP, total and conjugated bilirubin, and International Normalised Ratio (INR) within 2-5 days.

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Figure 9.3-1 Management of abnormal ALT



Other potential causes of liver toxicity must be evaluated, and subjects be monitored for development of any liver associated symptoms potentially indicative of DILI that include fatigue, nausea, new onset of or worsening or pruritus, jaundice, right upper quadrant pain, evidence of immunologic drug reaction manifested by rash or eosinophilia >5%, and/or hepatic decompensation manifested by fluid retention or encephalopathy.

Depending on the clinical context, recent infection with Epstein-Barr virus (EBV), herpes viruses, and toxoplasma should be considered. Additional tests such as anti-hepatitis A virus (HAV) IgM, hepatitis B core antibodies (anti-HBc) IgM (hepatitis B virus [HBV]-DNA if clinically indicated), anti-hepatitis C virus (HCV) and HCV RNA, anti-Cytomegalovirus (CMV) IgM and anti-hepatitis E virus (HEV) IgM antibodies should be considered. In case of suspicion of Gilbert Syndrome, a DNA diagnostic test should be considered.

If IMP administration is paused, subjects must be closely monitored for liver-related symptoms and have repeat measurement of liver biochemical tests within 2-5 days and, if abnormalities persist, then every 2 weeks until biochemical tests have returned to normal or baseline and/or or clinical resolution of any potential symptoms.

Baseline ALT is calculated as the average of the values obtained at screening and baseline prior to IMP administration.

<u>Criteria for discontinuation of IMP administration</u>

1. AE of Grade 4 or greater severity, other than AEs related to the primary disease, according to the Common Terminology Criteria for Adverse Events (CTCAE), or life-threatening AE if not covered by the CTCAE
2. Evidence of DILI as discussed above (Figure 9.3-1)

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3. Increase in ALP of > 2 x baseline, confirmed in a repeat testing, with liver symptoms
4. Platelet count of <50,000/µL, confirmed in a repeat testing
5. Clinically significant allergy or hypersensitivity reactions to golexanolone or placebo
6. GFR<30mL/min/1.73m^2 using the CKD-EPI equation, confirmed in a repeat testing
7. Increase of serum creatinine >2-fold from baseline, confirmed in a repeat testing
8. Hyponatremia defined as a Na ≤ 125mEq/L, confirmed in a repeat testing
9. Liver transplantation

9.3.9.3 Stopping rules for the study

If during a safety review by the SRC >15% of at least 40 subjects have met one of the individual stopping criteria in Section 9.3.9.2 (except liver transplant) or >2 subjects have met the same individual stopping criteria, resulting in premature, permanent discontinuation from study, enrolment may be halted until a final recommendation by the SRC regarding study conduct and continuation of enrolment is rendered to the Sponsor, as this could indicate severe adverse reaction(s). For this reason, a specific review of the safety data by the SRC, which could include breaking the randomisation code for individual subjects, would be necessary to advise on any change of study conduct or stopping the study. The cut-offs are based on possible natural variation/occurrences in the included population not exposed to Golexanolone. The SRC may recommend discontinuation of treatment for all participants during the safety review.

If the study is halted based on the stopping rules detailed in this section, the study can only be re-started after regulatory approval via a substantial amendment.

9.3.9.4 Subject replacement

Subjects who discontinue prior to first IMP administration may be replaced.

A treated subject withdrawn due to AEs will not be replaced.

Treated subjects withdrawn for other reasons than AE in Part A might be replaced, if recommended by the iSRC.

Subjects withdrawn for other reason than AE during Part B will be replaced, at the discretion of the Sponsor and if judged appropriate by the SRC, up to a maximum number of 11 subjects replaced.

9.4 Treatments

9.4.1 Identity of investigational medicinal product

Golexanolone will be supplied as a semi-solid lipid formulation in soft gelatine capsules intended for oral administration. Each capsule contains 10 mg golexanolone. The excipient is

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a mixture of mono -and diglycerides of caprylic and capric acid (Imwitor®), which is of pharmacopoeial quality.

Placebo capsules will contain the lipid excipient and be of identical appearance as the golexanolone capsules. The number of placebo capsules to be administered will be adjusted to match the number of golexanolone capsules administered on each dose level.

9.4.2 Packaging, labelling, and storage of investigational medicinal product

Bulk golexanolone and placebo capsules will be manufactured, packaged, and labelled by CCI [redacted].

Primary and secondary packaging and labelling of subject specific IMP kits will be performed by CCI [redacted].

Primary packaging

Capsules will be placed in thermoform blister strips containing golexanolone or placebo capsules (1 x 4 capsule format) in the configurations shown in Table 9.4-1. The configurations C and D will only be used if any adjustments of the anticipated dose levels for Part B are required based on evaluation of Part A data.

Table 9.4-1 Blister configurations

Blister type	Contents
A	4 placebo capsules
B	4 golexanolone 10 mg capsules
C	1 golexanolone 10 mg capsule + 3 placebo capsules
D	3 golexanolone 10 mg capsule + 1 placebo capsules

Blisters will be sealed into blister wallets in the configuration shown in Table 9.4-2. The Part B wallets will include IMP for 1 week BID dosing plus two additional days.

Table 9.4-2 Wallet configurations

Wallet type	Contents	Total no. of capsules/dosing
Part A 40 mg golexanolone	[1 B] x 2 (BID) x 5 (Days 1-5)	4
Part A placebo	[1 A] x 2 (BID) x 5 (Days 1-5)	4
Part B 40 mg golexanolone	[1 A + 1 B] x 2 (BID) x 9 (Days 1-7 + 2 extra)	8
Part B 80 mg golexanolone	[2 B] x 2 (BID) x 9 (Days 1-7 + 2 extra)	8
Part B placebo	[2 A] x 2 (BID) x 9 (Days 1-7 + 2 extra)	8

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Secondary packaging Part B

Wallets will be put into cartons including 4 wallets each with a unique kit number. At randomisation, a kit number will be allocated to a specific subject. Wallets will be dispensed to the subject on two occasions (Visit 2 and Visit 4).

Labels will comply with applicable Good Manufacturing Practice (GMP), with Annex 13 of the European Union Good Manufacturing Practice regulations and any local regulatory requirements.

All study medication must be stored in a safe place with limited access, at the temperature given on the labels (+2°C to +25°C). Temperature logs should be kept for the area where the IMP is stored at the clinic. The temperature should be noted on a daily basis (working days only unless automatic temperature readings are available).

Further information on handling and storage requirements of the IMP is provided in the IMP Manual.

9.4.3 Doses and treatment regimens

Part A

Subjects will be randomised to treatment with golexanolone 40 mg BID or placebo BID.

For subjects hospitalised according to the FULL PROCEDURE, all IMP will be administered at the study site under medical supervision with 240 mL water daily for 5 consecutive days, at approximately the same time each day.

For the MODIFIED PROCEDURE, the first dose (morning Day 1) and the last dose (evening Day 5) will be administered at the clinic. The remaining doses will be self-administered by the subject at home. The IMP will be swallowed with a glass of water before breakfast in the morning and, as far as possible, 2 hours after last meal in the evening. The subjects will be reminded daily by phone to take the IMP and the IMP intake will be registered daily in a Subject Diary.

The golexanolone dose of 40 mg BID, has been defined based on existing non-clinical and clinical data, as described in Section 9.2.2.

All subjects should be fasting overnight (8 hours) before administration on Day 1.
A standardised dinner will be served at the clinic 3 hours before the second daily dose on Day 5.

Part B

Subjects will be randomised to treatment with one of the anticipated golexanolone dose levels 40 mg BID, 80 mg BID (total daily dose 80 and 160 mg), or placebo BID.

The IMP will be swallowed with a glass of water daily for 28 consecutive days. The subjects will be instructed to administer the IMP before breakfast in the morning and, as far as possible, 2 hours after last meal in the evening.

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The subjects should be fasting overnight (8 hours) before the visit to the clinic on Days 1, 14, and 28 and the morning dose of IMP will be administered at the clinic these days.

9.4.4 Product accountability

The IMP will be released to the study sites after approvals of the CSP have been received from the IEC and the CA.

The IMP will be shipped to study sites as described in Section 6. The IMP will be dispensed to the study subjects at the site or from a local pharmacy, as applicable.

Subjects in Part B and subjects following the MODIFIED PROCEDURE in Part A will be instructed to return all used and unused IMP wallets to the clinic visits on Day 5 (Part A) and Day 14 and Day 28 (Part B).

The Investigator is responsible for keeping detailed records showing the quantity of IMP stored, delivered to, and taken out from the place of storage and IMP administered/dispensed to and returned by the subject. Any discrepancies between dispensed and returned IMP must be explained and documented. Products deliberately and/or accidentally destroyed by the Investigator or the subject must also be accounted for.

The Monitor will perform IMP accountability and verify that all unused IMP is adequately destroyed/returned and documented.

9.4.5 Method of assigning subjects to treatment groups

A computer-generated randomisation schedule will be prepared prior to the start of the study by the statistician at Accelsiors.

Randomisation will be performed via the electronic data capture (EDC) system after confirmation of subject eligibility on Day 1 (Visit 2), prior to first administration of IMP. Each subject will receive a unique randomisation number and will be allocated to respective treatment group according to the randomisation schedule.

In study Part A, subjects will be randomised 3:1 to golexanolone 40 mg BID or placebo BID.

In study Part B, subjects will be randomised 1:1:1 to one of the three treatment groups (anticipated golexanolone dose levels 40 mg BID, 80 mg BID, or placebo BID).

9.4.6 Blinding

This is a double-blinded study, and the allocation of treatments will not be disclosed until clean file has been declared and the database has been locked.

The identities of subjects will not be disclosed in the PK evaluation of Part A data. The pharmacokineticist will be un-blinded and will not participate in the decisions of the iSRC.

Treatment allocation will be blinded to the iSRC and SRC but can be un-blinded for individual subjects upon request (see Sections 9.1.4 and 9.1.5), following procedures pre-specified in the iSRC and/or SRC charters.

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Capsules of golexanolone and placebo will be of identical appearance. Placebo capsules will be used to make sure that the same number of capsules are given in all dose groups in Part B.

Accelsiors pharmacovigilance (PV) personnel will be un-blinded for SUSAR reporting purposes but are not involved in data analyses.

9.4.7 Emergency decoding of blinded treatment

Breaking the code must only be done in emergency situations when knowledge of the treatment is necessary for the proper management of the subject. A code breaking procedure with an audit trail will be available in the eCRF system (Zelta V2023.3.0.1 or higher). Decoding of the blinded treatment must be reported to Accelsiors and to the Sponsor.

9.4.8 Prior and concomitant therapy

If need emerges, medications considered necessary for the subject´s safety will not be withheld (including prohibited medications as listed in Section 9.4.8.2).

9.4.8.1 Allowed PBC standard of care medications

Treatment with SoC PBC medications, which may include UDCA, OCA, seladelpar, elfibranor, bezafibrate and/or fenofibrate, must be stable during the study.

9.4.8.2 Disallowed medications

The following medications will not be allowed during the study (Part A and B):

- Any other drug under investigation.
- Warfarin and warfarin-like anticoagulants.
- Regular use of prescribed or OTC medications that in the opinion of the Investigator are causing fatigue or cognitive dysfunction to the subject. Examples include benzodiazepines, sedating antihistamines (first generation), anticonvulsants, sedating antidepressants (e.g., tricyclic and sedating heterocyclic antidepressants), anticholinergics (benztropine), antiparkinsonian medications (amantadine, selegiline, benztropine), psychostimulants, narcotic medications.
- Hormonal contraceptives, other than IUS, transdermal (*e.g.* patches, gels and sprays) or local (*e.g.* vaginal tablets, gels, creams, rings, suppositories) administration of oestrogen or progesterone.
- Compounds sensitive to CYP3A4 inhibition/induction with a narrow therapeutic index, *e.g.:*
    - Amlodipine (calcium channel blocker)
    - Medicinal products that prolong the QT interval and are CYP substrates, such as dronedarone and domperidone

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- Ergot alkaloid derivatives, such as ergotamine and dihydroergotamine
- Examples of other prohibited CYP3A4 substrates: oral alfentanil, aprepitant, amiodarone, oral budesonide, buspirone, fentanyl, quetiapine, sildenafil, cyclosporine, quinidine, tacrolimus, docetaxel, everolimus, rivaroxaban and apixaban.

– Compounds sensitive to CYP2C19 inhibition with a narrow therapeutic index, *e.g.*:
  - Phenytoin

In addition to the above the following medications will not be allowed in study Part B:

– Statins metabolised via CYP3A4, e.g. atorvastatin, and simvastatin.

This list is not exhaustive and is intended to serve as guidance only. In general, the Summary of Product Characteristics (SmPC) for the co-medicated CYP3A4 and CYP2C19 substrates must be consulted for the recommendations regarding co-administration.

9.4.8.3 Medications with careful monitoring

The effects of metformin, which is an organic cation transporter 1 (OCT1) substrate, might be decreased by golexanolone. Therefore, blood glucose levels in subjects on metformin should be closely monitored.

9.4.9 Continuation of treatment

This is a phase 1b/2 study with the unregistered product golexanolone and thus there will be no treatment with golexanolone available after end of study participation.

9.4.10 Treatment compliance

For subjects hospitalised according to the FULL PROCEDURE in study Part A, all IMP will be administered at the study site under medical supervision to ensure compliance. For the MODIFIED PROCEDURE, the first dose (morning Day 1) and the last dose (evening Day 5) will be administered at the clinic. The remaining doses will be self-administered by the subject at home. The subjects will be reminded daily by phone to take the IMP and the IMP intake will be registered daily in a Subject Diary.

During the self-administration of IMP by subjects in Part B and by subjects following the MODIFIED PROCEDURE in Part A, the subject will be instructed to bring all used and unused IMP wallets to the clinic visits on Day 5 (Part A) and Day 14 and Day 28 (Part B), respectively. Intake of IMP will be registered in a diary on a daily basis. Plasma concentrations of golexanolone will be measured at each visit to the clinic from start of IMP administration to end of treatment.

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9.5 Study assessments

The timing and frequency of study visits and assessments in each study part are presented in the schedules of events (Table 9.1-1 to Table 9.1-8). Each study assessment is described in the sections below.

9.5.1 Recording of data and priorities

It is important that PK sampling in Part A occurs as close as possible to the scheduled time (± 10% up to the 24-hour post-dose time-point, thereafter ±3 hours). In order to achieve this, the timing priority order at a particular time point is:

1. Plasma samples for PK
2. Safety laboratory samples
3. ECG
4. Vital signs

The actual sampling time should always be recorded in the eCRF and will be used in the calculation of the PK parameters. Pre-dose efficacy assessments may be performed up to 90 minutes prior to dosing (if not specified in the schedule of events). The efficacy assessments must always be performed in the same order for a specific subject.

9.5.2 Demographics and other baseline characteristics

9.5.2.1 Informed consent

Signed informed consent must be obtained before any screening procedures are initiated. The informed consent procedure is further described in Section 5.3.

9.5.2.2 Demographic information

The following demographic data will be recorded: gender, age, race, and ethnic origin.

For WOCBP, date of onset of last menstrual period will be recorded.

9.5.2.3 Weight and height

Weight and height will be measured without shoes. Body mass index (BMI) will be calculated from the height and weight recorded and rounded to the nearest whole number.

9.5.2.4 Medical/surgical history

Medical/surgical history will be obtained by interview for verification of eligibility criteria.

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9.5.2.5 Prior and concomitant medications

Medication history (prior medications) from 4 weeks prior to screening until administration of the first dose of IMP will be recorded in the eCRF. Prescription medications, OTC medications, and herbal products should be asked for.

Any medication used from first administration of IMP until the last follow-up assessment (concomitant medications) will be recorded in the eCRF.

9.5.2.6 HIV and hepatitis B/C

Subjects will be tested for HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen, HBV surface antigen and HCV antibodies at screening in order to protect the personnel handling the blood samples.

9.5.2.7 Alcohol breath test

An alcohol breath test will be performed at time-points specified in Section 9.1. Additional random tests can be performed during the study period.

9.5.2.8 Practice for cognitive tests

To mitigate learning/familiarisation effects when using the cognitive tests, all cognitive tests will be administered by trained raters at screening for Part B.

Cognitive test performance at screening will be recorded in the eCRF for quality control purposes.

9.5.3 Clinical safety assessments

Any abnormalities will be specified and documented as clinically significant or not clinically significant.

Pre-dose clinically significant abnormalities will be recorded as medical/surgical history if related to a condition pre-existing the signing of the ICF and as an AE if related to a condition following the signing of the ICF.

Post-dose abnormalities not present pre-dose and judged as clinically significant by the Investigator will be reported as AEs.

9.5.3.1 Physical examination

A physical examination will include assessments of the lungs, cardiovascular, and abdomen.

9.5.3.2 Vital signs

Systolic and diastolic BP and pulse will be measured in the supine position after 10 minutes of rest. Body temperature will be measured using local routine methods at each study site.

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9.5.3.3 Resting 12-lead ECG

Single 12-lead ECGs will be recorded in supine position after 10 minutes of rest. Heart rate and PR, QRS, QT and QTcF intervals will be recorded. ECGs will be reviewed and interpreted on-site by the Investigator.

If the automated ECG software reporting values are considered inaccurate by the Investigator, the parameter will be measured manually by the Investigator and recorded on the ECG strip.

9.5.3.4 Hospital Anxiety and Depression Scale

The HADS is a self-report questionnaire designed to screen anxious and depressive states in patients in non-psychiatric settings.

The HADS is a 14-item scale with seven of the items relating to anxiety and seven relating to depression [20, 21]. Each item is rated on a 4-point scale, ranging from 0 to 3, with 3 indicating higher symptom frequency. Total scores for each subscale range from 0 to 21, using the following categorisation:

0-7 = Normal

8-10 = Borderline abnormal (borderline case)

11-21 = Abnormal (case)

The scale was originally developed for use in a hospital setting, although it is now widely used across all settings, including screening in normal population. The scale avoids reliance on aspects of these conditions that are also common somatic symptoms of illness (*e.g.* fatigue and insomnia or hypersomnia, irritability, poor concentration).

The subject is given the following instruction:

Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't take too long over you replies: your immediate is best.

9.5.4 Laboratory safety assessments

Blood samples for analysis of clinical chemistry, haematology, and coagulation parameters will be collected through venepuncture or an indwelling venous catheter. Samples will be analysed by routine analytical methods at GBA Central Lab Services GmbH. Reference ranges from the central laboratory will be used.

Urine analysis will be performed at the clinic using dipsticks.

A serum pregnancy test will be performed for all WOCBP at screening (Visit 1) and a urine dipstick test will be performed as specified in Table 9.1-1 and Table 9.1-8 (Section 9.1).

The samples will be registered in a tissue-bank, where required by local legislation, and any remains will be disposed of after analyses.

Parameters to be analysed are defined in Table 9.5-1.

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Table 9.5-1 Safety laboratory parameters

Category	Parameter
Clinical chemistry	Albumin
	Alanine aminotransferase (ALT)[1]
	Alkaline phosphatase (ALP) [1]
	Aspartate aminotransferase (AST)
	B12[4]
	Bilirubin (total and conjugated)[1]
	Creatinine[1]
	Cystatin C
	Folate[4]
	Glucose *(Part B only)*
	Potassium[1]
	Sodium[1]
	Thyroid-stimulating hormone (TSH)[2]
	Free triiodothyronine (FT3)[2]
	Free thyroxine (FT4)[2]
	FSH[3]
	Oestradiol[3]
Haematology	Haematocrit[1]
	Haemoglobin (Hb)[1]
	Platelet count[1]
	Red blood cell (RBC) count
	White blood cell (WBC) count with differentials[1]
Coagulation	International Normalised Ratio (INR) [1]
Urinalysis (dip stick)	Glucose
	Hb/erythrocytes
	Nitrite
	Protein
Pregnancy test	Serum pregnancy test

[1] The limited panel consists of these parameters only
[2] At the screening visit and pre-dose Day 1 only
[3] At screening in questionable cases, post-menopausal females only
[4] At the screening visit, Visit 6, and Visit 7 only

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9.5.5 Adverse Events

9.5.5.1 Definitions

Adverse event

An AE is any untoward medical occurrence in a clinical study 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 clinically significant abnormal values from relevant tests, such as clinical safety laboratory tests, ECGs, vital signs), symptom, or disease temporally associated with the use of an IMP, regardless of whether it is considered related to the IMP.

Clarifications:

Symptoms or findings from the physical examination obviously attributable to the pre-existing PBC diagnosis should be considered as medical history and not reported as AEs unless worsening unexpectedly.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as “acute appendicitis” and the resulting appendectomy noticed under *Comments*. Pre-study conditions, which led to elective surgery during the time of the study, are not to be reported as AEs.

If an abnormal laboratory value or vital sign is associated with corresponding clinical signs and symptoms, the sign/symptom should be reported as the AE and the associated laboratory result or vital sign should be considered additional information that is to be collected in the eCRF.

Serious adverse event

A serious adverse event (SAE) is any AE that:

- results in death
- is life-threatening (this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe)
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- results in a congenital anomaly/birth defect
- is medically important (this refers to an event that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent any of the SAEs defined above)

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Examples of medically important events are intensive treatment in an emergency room for allergic bronchospasm or blood dyscrasias, convulsions that do not result in hospitalisation, development of drug dependency and drug abuse.

Planned hospitalisations or surgical interventions for a condition that existed before the subject signed the ICF and that did not change in intensity are not SAEs.

If there is any doubt as to whether an AE meets the definition of an SAE, a conservative viewpoint must be taken, and the AE must be reported as an SAE.

Serious adverse reaction

The term serious adverse reaction (SAR) is to be used whenever either the Investigator or Sponsor or designee assessed the SAE as possibly or probably related to the IMP.

Suspected unexpected serious adverse reaction

A SUSAR is any SAR whose nature or intensity is not consistent with the current version of the Investigator's Brochure for golexanolone [3].

9.5.5.2 Assessment of intensity/severity

The grading of the intensity/severity of AEs will follow the CTCAE [32]. Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline.

The Investigator must assess the *intensity/severity* of an AE using the following definitions, and record it on the AE Log of the eCRF:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self- care ADL**
Grade 4	Life-threatening consequences: urgent intervention indicated
Grade 5	Death related to AE

** Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.*

***Self- care ADL refer to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.*

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9.5.5.3 Assessment of causality

The Investigator must assess the *causal relationship* between an AE and the IMP using the definitions below and record it on the AE Log of the eCRF:

Probable	The event has a strong temporal relationship to the IMP or recurs on re-challenge, and another aetiology is unlikely or significantly less likely.
Possible	The event has a suggestive temporal relationship to the IMP, and an alternative aetiology is equally or less likely.
Unlikely	The event has no temporal relationship to the IMP or is due to underlying/concurrent illness or effect of another drug (that is, there is no causal relationship between the IMP and the event).
NA	Assessment not applicable for events occurring before first dose of IMP.

An AE is considered causally related to the use of the IMP when the causality assessment is *probable* or *possible*.

9.5.5.4 Assessment of outcome

The Investigator must assess the *outcome* of an AE using the definitions below and record it on the *Adverse Event Form* in the eCRF:

Recovered/resolved	The subject has recovered completely, and no symptoms remain.
Recovering/resolving	The subject's condition is improving, but symptoms still remain.
Recovered/resolved with sequelae	The subject has recovered, but some symptoms remain (for example, the subject had a stroke and is functioning normally but has some motor impairment).
Not recovered/not resolved/ongoing	The subject's condition has not improved, and the symptoms are unchanged (for example, an atrial fibrillation has become chronic).
Fatal	The subject died.
Unknown	Assessment not possible.

9.5.5.5 Methods for eliciting adverse events

AEs identified using any of the following methods will be recorded:

- AEs spontaneously reported by the subject
- AEs observed by the Investigator or medical personnel
- AEs elicited based on non-leading questions from the Investigator or medical personnel

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For AE reporting purposes, no distinction should be made between the active product and placebo as long as the blinding is not broken.

9.5.5.6 Recording of adverse events

Collection of AEs starts after the subject signed the ICF and continues until the last follow-up assessment. Adverse events occurred after first administration of IMP will be defined as treatment emergent AEs (TEAEs).

If no AE has occurred during the study period, this should be stated in the eCRF.

The study personnel will record in the eCRF and medical records any medical events occurring from screening to the last follow-up assessment, whether observed by the Investigator or reported by the subject. Any AE with start date on the day of first IMP administration must be recorded with start time.

If the AE is serious, this must be indicated in the eCRF and reported as described in Section 9.5.5.7.

AEs, including out-of-range clinically significant clinical safety laboratory values, must be recorded individually, except when considered manifestations of the same medical condition or disease state; in such cases, they must be recorded under a single diagnosis.

If the intensity of an AE increases the event information needs to be updated in the eCRF.

9.5.5.7 Reporting of serious adverse events

Starting from signing of the ICF, all SAEs must be reported by the Investigator within 24 hours of awareness via the eCRF. No distinction should be made between the investigational product and the reference product regarding reporting of SAEs as long as the code is not broken.

SAEs spontaneously reported by a subject to the Investigator within 30 days after the last follow-up assessment must be handled in the same manner as SAEs occurring during the study.

9.5.5.8 Reporting of SUSARs to EudraVigilance, local CA and IEC

The term SAR is used whenever either the Investigator or the Sponsor or delegate deems a blinded SAE as possibly or probably related to IMP. If a SAR is assessed as unexpected, it is a potential SUSAR and a certified EudraVigilance reporter will be unblinded. In case the event is regarded as a SUSAR the EudraVigilance reporter will report the SUSAR to the CA, via the EudraVigilance database, and to the IEC in accordance with local regulations and Accelsiors standard operating procedures (SOPs) within the following timelines:

- 7 calendar days if fatal or life-threatening (follow-up information within an additional 8 days)

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- 15 calendar days if non-fatal and non-life-threatening (follow-up information as soon as possible)

The clock for expedited initial reporting (Day 0) starts as soon as the Sponsor or delegate has received the information containing the minimum reporting criteria. The date should be documented on an acknowledgement of receipt.

In case of disagreement between the Investigator and Sponsor or delegate in terms of the causality judgement, the causality must never be downgraded.

The Sponsor or delegate is responsible for informing all Investigators concerned of relevant information about SUSARs that could adversely affect the safety of study subjects. The appropriate IEC and CA, as per local requirements, should be informed by the Sponsor about SAEs associated with the use of the product (SUSARs).

The Sponsor or delegate is responsible for once a year throughout the clinical study (or on request), submit a safety report to the CA and the IEC including all new available safety information received during the reporting period.

9.5.5.9 Treatment and follow-up period of adverse events

Subjects with AEs occurring during the study must be treated according to daily clinical practice at the discretion of the Investigator.

All AEs must be followed up until resolution or the follow-up assessment, whichever comes first. At the follow-up visit, information on new AEs, if any, and stop dates for previously reported AEs must be recorded (if known). Only AEs assessed as related to the IMP which are ongoing at the follow-up visit must be followed up until resolution/stabilisation.

It is the responsibility of the Investigator to follow up on all SAEs until the subject has recovered, stabilised, or recovered with sequelae, and to report to the Sponsor all relevant new information using the same procedures and timelines as those for the initial report. Relevant information includes discharge summaries, autopsy reports, and medical consultation.

9.5.5.10 Procedures in case of pregnancy

In case of pregnancy or suspicion of possible pregnancy, the study treatment must be stopped immediately, and the subject discontinued from participation in the study. Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP may have interfered with the effectiveness of the contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even after the subject was discontinued from the study.

All events of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as AEs. All outcomes of pregnancy must be reported to Accelsiors PV team via e-mail (PVTeam@accelsiors.com) on the pregnancy outcomes report form.

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The baby should be followed for 2 weeks after the delivery, or until the first well-baby visit, whichever comes first.

9.5.6 Pharmacokinetic assessments

9.5.6.1 Sample collection and handling

Determination of concentrations of golexanolone will be made in plasma. Venous blood samples (approximately 5 mL) will be collected at the specified time-points (see Table 9.1-1 to Table 9.1-8; Section 9.1). The date and time of collection of each sample will be recorded in the eCRF.

The samples will be registered in a tissue-bank, where required by local legislation, and stored at -70°C until analysed. The samples will be disposed of after the clinical study report has been finalised.

Urine will be collected during the time interval presented in the schedule of events.

One aliquot of plasma and urine will be sent to MetaSafe AB, Sweden for metabolite screening. The decision to analyse these samples or not will be based on PK results in plasma, when available. Should PBC subjects have a PK-profile that deviates from those previously determined in healthy volunteers and subjects with liver cirrhosis, a decision to analyse metabolite profile in plasma and urine will be made. The analysis results will be presented separately from the clinical study report.

Detailed instructions for collection, handling, labelling, storage, and shipment of samples will be provided in the Laboratory Manual.

9.5.6.2 Analysis of plasma samples

Samples for determination of concentrations of golexanolone in plasma will be analysed by Lablytica Life Science AB, Sweden by means of a validated LC-MS/MS method. The details of the analytical method used will be described in a separate bioanalytical report.

9.5.7 Clinical efficacy assessments

9.5.7.1 PBC-40

The PBC-40 is a patient-derived, disease specific HRQoL measure developed and validated for use in PBC [5].

The characteristics of the measure have been described in detail and it has been widely applied in practice [4, 33, 34, 35, 36, 37]. It is designed for self-completion and takes approximately 5 minutes to complete.

The paper questionnaire consists of 40 questions, each scored on a scale of 1 to 5 (where 1=least impact, 5=greatest impact) grouped into six domains (cognition, itch, fatigue, social, emotional, and general symptoms). For each domain, scoring involves summing individual question response scores, range of 6-30. Higher scores indicate a poorer quality of life.

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The original version of the PBC-40 with a 4-week recall period will be used at screening. An adaptation of the PBC-40 to a weekly recall period will be used at subsequent study visits [38].

The subject is given the following instruction:

For each statement, please indicate the response that comes closest to how you feel. If any of the statements do not apply to you, please indicate 'does not apply.

9.5.7.2 EQ-5D-3L

The EQ-5D tool is a standardised measure of health status developed by the EuroQol Group to provide a simple, generic measure of health for clinical and economic appraisal [39].

The EQ-5D three-level version (EQ-5D-3L) essentially consists of two pages: the EQ-5D descriptive system and the EQ-5D visual analogue scale (EQ VAS):

- The EQ-5D-3L descriptive system comprises the following five dimensions, each describing a different aspect of health: MOBILITY, SELF-CARE, USUAL ACTIVITIES, PAIN / DISCOMFORT and ANXIETY / DEPRESSION. Each dimension has three levels: no problems, some problems, extreme problems (labelled 1–3). The respondent is asked to indicate his/her health state by checking the box against the most appropriate statement in each of the five dimensions.
- The EQ VAS records the respondent's self-rated health on a vertical VAS where the endpoints are labelled *The best health you can imagine* and *The worst health you can imagine*. This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

For both the descriptive part of the questionnaire and the VAS, the subject is asked to rate the health of TODAY.

An EQ-5D summary index is derived by applying a formula that essentially attaches values (weights) to each of the levels in each dimension.

A paper version will be used.

9.5.7.3 Epworth Sleepiness Scale

The ESS is a validated self-administered questionnaire for assessment of daytime hypersomnolence [22]. Respondents are asked to rate, on a 4-point scale (0-3), their usual chances of dozing off or falling asleep while engaged in eight different activities (*i.e.* eight questions). The ESS score (the sum of eight item scores, 0-3) can range from 0 to 24. The higher the ESS score, the higher that person's average sleep propensity in daily life, or their 'daytime sleepiness'.

A paper version of the questionnaire will be used. The questionnaire takes no more than 2-3 minutes to answer.

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Interpretation of the scores:

0-5	Lower Normal Daytime Sleepiness
6-10	Higher Normal Daytime Sleepiness
11-12	Mild Excessive Daytime Sleepiness
13-15	Moderate Excessive Daytime Sleepiness
16-24	Severe Excessive Daytime Sleepiness

9.5.7.4 Portosystemic Hepatic Encephalopathy Score

The PHES is a paper-pencil test battery for the assessment of covert HE [23, 24, 25]. It is the only cognitive test battery that has been validated for hepatic indications. However, since cognitive test performance is typically more impaired in covert HE than in PBC, for this study the PHES will be supplemented with additional measures of memory and verbal fluency (see Sections 9.5.7.5 and 9.5.7.6).

The PHES is composed of five sub-tests, number connection test-A (NCT-A), number connection test-B (NCT-B), serial dotting test (SDT), line tracing test (LTT) and digit symbol test (DST). PHES assesses motor speed, motor accuracy, concentration, attention, visual perception, visual-spatial orientation, visual construction, and memory, which are related to most of neuropsychological impairments in CHE.

There are 4 versions of the PHES sub-tests. The same version should be used at Visit 2 (baseline) and Visit 6 (end of treatment). Two different versions should be used at Visit 1 (screening) and Visit 4, to avoid learning effect.

The subject is given a short, standardised instruction to each of the five subtests and completes them one at a time under supervision. To make sure the subject has understood correctly, training tests are completed for the NCT-A, the SDT, LTT and DST tests.

Scoring of the PHES: The time (sec) spent on each test is noted and converted into a score as indicated in the age-adjusted normal values. A score of zero is given for a subtest performance within +/- 1 standard deviation (SD). The maximum score is +1 while the lowest possible score is -3 (-3 SDs). Note that two scores are assigned for the LTT: A time score and an error score. The sum of the 6 sub-scores is the PHES and is abnormal when below -4. The PHES range is -18 – 6. Testing and scoring take approximately 15 minutes.

9.5.7.5 Rey Auditory Verbal Learning test

The RAVLT is a validated word list learning task composed of 15 words that are read to the subject at a rate of one word/second after which the subject is asked to recall as many words as they can. This procedure is repeated five times. The sum of words recalled across these five trials constitutes the immediate recall score. This is a common testing paradigm for the measurement of verbal episodic memory. The RAVLT is a widely used test, originally adapted from the French in 1959 [26].

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The RAVLT will be given before the PHES (as a measure of learning). After completion of the PHES, the RAVLT delayed recall test will be given in which the subject is asked to recall as many words from the list as possible after the delay.

There are several equivalent forms permitting alternation between forms for repeated administration. The form used at visit 2 (Baseline) should be same as form used at Visit 6 (end of treatment).

Administration time for both immediate and delayed forms is 8-10 minutes.

9.5.7.6 Delis and Kaplan Executive Function System Letter and Category fluency subtests

The Category Fluency and Letter Fluency tests from the D-KEFS are validated ideational fluency tasks in which the subject is asked to say as many words as possible in 1 minute that adhere to a particular rule.

For the Category Fluency task, first the subject is asked to name as many animals as they can in 1 minute. Then a second category is provided (boy's names). The score is the sum of the number of words provided in the two categories. An alternative version using two different and equivalent categories will be given at alternating visits.

Letter Fluency requires the subject to say as many words as possible beginning with a target letter in 1 minute. The number of words generated in three trials with three different letters are summed. Constraints are given (*e.g.* no proper names, no numbers) and only words within those rules are counted as correct.

Together these tests take 6-7 minutes to administer and another 3 minutes to score. For both the Letter and Category fluency tasks there are two equivalent forms that can be alternated. The form used at Visit 2 (Baseline) should be same as form used at Visit 6 (end of treatment). The alternate form can be used at Screening and Visit 4.

9.5.7.7 Clinical global impression of severity and change-PBC version

The clinical global impression (CGI) scale consists of two clinician-rated instruments, CGI-S-PBC and CGI-C-PBC, respectively measuring overall disease severity and change. A PBC-specific version has been developed based upon extensive qualitative work in PBC of Jacoby 2005 [5] that underpins the well validated PBC-40 and employing these domains and questions in a semi-structured clinical interview format with anchored clinician ratings. This PBC specific version of the CGI-S and CGI-C is undergoing validation.

Since its first publication the CGI has become one of the most widely used assessment tools in psychiatry [40]. For example, the CGI, especially the CGI change scale (CGI-C) has been widely utilised as an efficacy measure in clinical drug trials in different mental disorders [*e.g.* depression, schizophrenia; [41, 42]. Its popularity is mainly based on its ability to capture a well-informed overall clinical impression, even in disease states where the presentation is heterogeneous.

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In psychiatric indications, the CGI is administered after completing several standardised semi-structured interview instruments to survey symptoms and their severity, thus assuring that CGI ratings are based upon a uniform examination of the subjects across raters, sites, and visits. Reliable use of a CGI in the absence of preceding clinical rating scales can be achieved by conducting disease-specific semi-structured interview [43].

The CGI-S-PBC entails a 30-45 minute semi-structured interview examining all six clinical domains identified as clinically relevant for patients living with PBC. Domain-specific and global ratings are rendered by trained independent clinical raters who are experts in PBC and have been certified for this purpose to be central raters. All CGI-S-PBC and CGI-C-PBC interviews will be video-recorded and used to support the evaluation made by the raters.

The CGI-S-PBC interview will be performed at baseline and again after 4 weeks *(exploratory endpoint)*. For the 4 weeks assessment, extensive observational notes, video-recording, and subdomain ratings from the baseline CGI-S-PBC will be reviewed by the rater before the interview for CGI-S-PBC and CGI-C-PBC are conducted so that ratings of change are well informed by the degree of severity and symptom profile observed prior to treatment. A second qualified rater, fluent in the language of the interview, will use the video-recordings to make an independent rating of the interview (CGI global and all domains) within 1 week of the original interview. The raters will enter the final ratings of the CGI-S-PBC and CGI-C-PBC into the eCRF.

The subjects will have to consent to the video-recordings by signing the ICF. Detailed instructions for the interviews, evaluations and data handling will be available in a study-specific manual.

9.5.8 Exploratory assessments

9.5.8.1 Plasma levels of neurosteroids and pro-inflammatory biomarkers

Blood samples for analysis of plasma levels of neurosteroids (*e.g.* allopregnanolone) and pro-inflammatory biomarkers (*e.g.* cytokines, chemokines, bile acids) will be collected in study Part B. The samples will be registered in a tissue-bank, where required by local legislation, and stored at -70°C until analysed at the end of the study.

The samples will be analysed by Admescope Ltd, Oulu, Finland. The details of the analytical method used will be described in a separate bioanalytical report.

The samples will be disposed of when analysed and reported.

Detailed instructions for collection, handling, labelling, storage, and shipment of samples will be provided in the Laboratory Manual.

9.5.8.2 Clinical global impression of severity and change-PBC version

See Section 9.5.7.7.

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9.6 Appropriateness of measurements

All methods used for safety assessments are commonly used in standard medical care and in early clinical studies.

The secondary endpoint change from baseline in the cognitive domain of PBC-40 at Day 28 was chosen as the basis of sample size estimation. PBC-40 is a disease specific HRQoL measure developed and validated for use in PBC [5].

9.7 Data quality assurance

This study will be conducted in compliance with the CSP, relevant SOPs, GCP and applicable regulatory requirements.

The Principal Investigator at each site will provide the Sponsor with all data produced during the study from the scheduled study assessments. He/she ensures the accuracy, completeness, legibility, and timeliness of the data reported to Sponsor in the eCRF and in all required reports.

During CSP development, the Sponsor has identified those processes, systems (facilities, computerised systems) and data that are critical to ensure human subject protection and the reliability of study results according to applicable SOPs and ICH E6 R2. Identified risks and mitigation actions are categorised and documented separately from the CSP, including risks associated with the COVID-19 pandemic.

Sponsor oversight responsibilities, such as monitoring, AE reporting, safety monitoring, changes in Investigators and key study team staff and quality assurance activities may need to be re-assessed in relation to the COVID-19 pandemic and temporary, alternative proportionate mechanisms of oversight may be required. An updated risk assessment will be performed prior to enrolment of the first subject.

9.7.1 Monitoring

The study site will be visited by the Monitor and/or the Project Manager periodically at times agreed on by the Investigator and Accelsiors. It is the function of the Monitor to ascertain that all aspects of the CSP are complied with and that the conduct of the study conforms to applicable regulatory requirements and established rules for GCP.

At the time of each monitoring visit, the Monitor will review the completed eCRFs to ascertain that all items have been completed and that the data provided are accurate and obtained in the manner specified in the CSP.

The Monitor will also check that the data in the eCRF are consistent with the clinical records (Source Data Verification [SDV]) and that study results are recorded completely and correctly. The Monitor will check on the reporting of SAEs and the procedures for IMP accountability and record keeping. For this purpose the Monitor must be given direct access to clinical records, original laboratory data, etc., as far as these relate to the study and without

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jeopardising subject integrity. The eCRFs for all subjects enrolled must be made available to the Monitor for review.

9.7.1.1 Risk-based monitoring

Risk-based monitoring including reduced SDV, triggered monitoring, centralised monitoring, and targeted monitoring will be conducted (EMA Reflection Paper 2013, FDA Guidance for Industry 2013, EMA Guidance 2020, FDA Guidance 2020). All critical data will require SDV by the Monitor and critical data will be identified in advance, to ensure subject's safety and the reliability of study results. The extent and details of monitoring including SDV will be described in the Clinical and Central Monitoring Plans.

Depending on the COVID-19 pandemic situation at the study site, site qualification and initiation visits may be performed remotely.

During the study, regular monitoring visits will be performed according to ICH GCP, and Accelsiors' SOPs, and local regulations. The frequency and type of monitoring visits will depend amongst other factors on the study site's recruitment rate and current pandemic situation in each country and study site.

Physical monitoring visits at the study sites may not be feasible or may be restricted for some time due to the COVID-19 pandemic situation, and either a combined remote and on-site monitoring or full remote monitoring visit will be conducted during these periods. The Sponsor authorises Accelsiors to include remote monitoring visits according to the applicable guidelines and regulations into the monitoring activities. In line with local laws and regulations, remote SDV might be part of the remote monitoring visits and if so, it has to be agreed between the Sponsor designee, the Investigator, and additional investigational staff at each study site. The relevant study documents (*e.g,* Monitoring Plans) will be adjusted to reflect these activities that will be held during the period when standard monitoring visits are not feasible.

Prior to site activation, the CRA will ensure a procedure is agreed with each investigational site to ensure remote SDV in case of SARS-COV-2 crisis. For remote monitoring purposes, no medical records may be sent, even if pseudonymised.

The ICH GCP requirements and applicable data protection and privacy regulations must be met in any case and for any selected monitoring approach. As part of the ICF, the subjects need to agree to a remote monitoring of data.

9.7.2 Audits and inspections

The study site may also be subject to quality assurance audit by the Sponsor, or someone appointed for this task by the Sponsor. A CA may announce an inspection of the study site. The procedures of such a visit would be similar to those of a monitoring visit, and data already checked by the Accelsiors Monitor may be checked again. The Investigator is required to inform Accelsiors and the Sponsor immediately of an inspection requested by a CA.

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9.7.3 Source documents

Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verifies the existence of the subject, the inclusion and exclusion criteria, and all records covering the subject's participation in the study. Source documents include laboratory notes, memoranda, material dispensing records, subject files, etc. The eCRF is considered as source data when data is entered directly into the eCRF.

A separate source data document will be generated at the study site before start of enrolment, specifying the location of the source of derived information appearing in the eCRF. This document must be signed by the Principal Investigator and the Monitor to confirm agreement before start of recruitment.

The Investigator should guarantee access to source documents and eCRFs for the Monitor, CA, and the IECs, as required.

9.7.4 Training of study staff

Before enrolment of subjects the Monitor and/or Project Manager will perform a study initiation visit at each study site. The requirements of the CSP and related documents will be reviewed and discussed, and the investigational staff will be trained in any study-specific procedures and systems utilised.

It is the responsibility of the Principal Investigator to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study and have a detailed knowledge of and training in the procedures that are to be executed by them. Any new information of relevance to the performance of this study must be forwarded to the staff involved in a timely manner.

The Principal Investigator will keep a list of all personnel involved in the study together with their function and study-related duties delegated. A curriculum vitae will be available for all staff to whom study-specific duties are delegated.

9.8 Statistical methods and determination of sample size

The principal features of the statistical analyses to be performed are described in this section. A more technical and detailed elaboration of the analyses will be presented in a separate statistical analysis plan, which will be signed and approved prior to database lock.

Statistical analyses will be performed by Accelsiors Ltd.

9.8.1 General considerations

All statistical calculations will be performed using the SAS® program version 9.4 (SAS Institute Inc., Cary, NC, USA) or above. The statistical analyses will include descriptive statistics reflecting the explorative nature of the study. In general, the data will be presented

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by treatment arm. The data for subjects receiving placebo will be presented pooled across groups.

Continuous data, other than PK data, will be summarised by treatment arm, displaying the number of available measurements, arithmetic mean, standard deviation (SD), median, minimum, and maximum. Categorical data will be summarised by treatment arm, and as a minimum the number and percentage of subjects in each category will be presented.

Descriptive statistics for the PK parameters will be presented by dose-level with number of measurements, arithmetic mean, SD, coefficient of variation (CV), median, minimum, maximum, geometric mean, geometric CV%.

In general, P-values will be interpreted descriptively, except for the cognitive domain of PBC-40 which was chosen as the basis of sample size calculation, and where the overall type I error rate will be preserved by applying a hierarchical testing procedure.

9.8.2 Determination of sample size

The primary objective of this study is to assess the safety and tolerability of treatment with 40 mg BID of golexanolone for 5 days (Part A) and with 40 and 80 mg BID for 28 days (Part B). With 28 subjects per treatment arm in Part B, the underlying true incidence of rare AEs which didn't occur in an active treatment arm during the study does not exceed 10%, with a probability of 95%.

The main efficacy objective in study Part B is to estimate the effect sizes for different secondary efficacy endpoints to enable a well-founded choice of the primary efficacy endpoint for the phase 3 confirmatory study. One of the secondary endpoints, change from baseline in the cognitive domain of PBC-40 at Day 28 was chosen as the basis of sample size estimation.

From data in PBC-UK, an estimate of the SD for the PBC-40 cognitive domain, restricted to those who meet the study inclusion criteria was 4.1. This result was also confirmed by Hirschfield [44], where the SDs of changes from baseline in PBC-40 cognitive domain score were 4.0 and 3.0 in the active treatment arm and placebo, respectively. Therefore, in the current sample size evaluation an SD of 4.0 for change from baseline was assumed for all treatment arms. PBC-40 cognitive domain has a range of 6–30 score with 6 being normal functioning. It is assumed that an efficacious dose would have a mean (SD) decrease of 3 (4.0) points compared to placebo.

The analysis of changes from baseline in PBC-40 cognitive domain scores is planned to be performed within an analysis of covariance (ANCOVA) model accounting for treatment arm and baseline PBC-40 score as a continuous covariate. Least-square mean differences (95% analysis of covariance [CIs]) between active treatment arms and placebo will be estimated within this ANCOVA framework. Although the main objective of the efficacy analysis is the estimation of effect size within the ANCOVA model, the study will be powered for the comparison between the highest dose and placebo arm.

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The power is thus evaluated for the comparison of the highest dose against placebo, assuming a 3-point difference between means, and a common between-arm SD of 4.0 points. Twenty-eight evaluable subjects per treatment arm (overall N=84) will provide approximately 79.2% power for this comparison, and 82.0% power to conclude a significant overall treatment effect in the analysis of variance (ANOVA) model at a 0.05 significance level. The power estimation was performed by *proc glmpower* in SAS® version 9.4.

When approximately 60 subjects from Part B completed Day 28 (*i.e.* 20 subjects per treatment arm), an interim analysis will be performed for sample size re-assessment. The originally planned overall sample size will not be decreased and no possibility for early stopping (for futility or for efficacy) is defined. The maximum overall sample size is set to 126 (a 1.5-fold increase compared to the originally planned sample size of 84).

The sample size re-estimation will be based on conditional power (CP) according to the method outlined in Chen, 2004 [1], targeting a CP of 80%. The promising zone for the CP calculated based on the observed data at the interim (CP_{obs}) ranges from 39% to 80% for this study design, therefore the sample size will be re-calculated only if CP_{obs} is contained in this range. By this procedure the overall type I error rate will be preserved.

The distribution of the overall final sample size was assessed by simulating 10000 cases with the conditions of the original sample size evaluation (difference between means equals to 3 points, SD equals to 4). The sample size is expected to be adjusted in approximately 17% of the cases, and in around 5.7% of the cases it will be higher than the maximum of 126, therefore it will be truncated to 126. The expected value and quantiles of the overall sample size are presented in Table 9.8-1.

Table 9.8-1 Distribution characteristics of the final overall sample size

Mean	**Minimum**	**Q1**	**Median**	**Q3**	**Maximum**
88.5	84	84.0	84.0	84.0	126

9.8.3 Analysis data sets

The Intent-to-Treat (ITT) analysis set will comprise all randomised subjects.

The Modified ITT (mITT) analysis set will comprise all subjects from ITT having baseline and at Day 28 measurement for at least one secondary efficacy endpoint.

The Per Protocol (PP) analysis set will comprise all subjects from mITT, with no major protocol deviations affecting efficacy.

The PK analysis set will comprise all subjects with at least one evaluable PK profile.

The Safety analysis set will comprise all subjects who received at least one dose of the IMP.

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9.8.4 Description of study population

Demographics, baseline characteristic, medical/surgical history, concomitant medications, and treatment compliance will be presented descriptively. All data will be listed.

Medical/surgical history will be summarised by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT).

Prior and concomitant medications will be coded according to the WHO Drug Dictionary and presented by Anatomic Therapeutic Chemical (ATC) classification system level 4.

9.8.5 Analysis of safety parameters

All safety data will be listed. Analysis will be performed on the Safety Analysis Set.

Target population: Subjects with non-cirrhotic or Child-Pugh class A PBC subjects with clinically significant fatigue and cognitive symptoms, fulfilling the enrolment criteria.

Variable of interest (Part A): Number of observed safety events during the 5-days treatment period in each treatment arm.

Variable of interest (Part B): Number of observed safety events during the 28-days treatment period in each treatment arm.

Intercurrent events (ICE): treatment discontinuation for any reason or use of disallowed medications treatment policy strategy.

Population-based summary statistics: proportion of subjects with AEs in each treatment arm.

Definition of the secondary estimands will be provided in the statistical analysis plan.

9.8.5.1 Physical examination

Clinically significant and non-clinically significant abnormal findings will be specified and presented by subject.

9.8.5.2 Vital signs

Vital signs (BP, pulse, and body temperature) will be summarised by treatment arm, using descriptive statistics, and including absolute change from baseline. Shift tables will be prepared.

9.8.5.3 Electrocardiogram

All ECG data will be summarised by treatment arm. In addition, ECGs will be categorised as "normal", "abnormal, not clinically significant", or "abnormal, clinically significant" (as judged by the Investigator) and summarised by treatment arm and shift tables will be prepared.

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9.8.5.4 Hospital Anxiety and Depression Scale

Mean and individual change in HADS scores from baseline to end of treatment will be summarised by treatment arm. Results will be analysed within an ANCOVA model accounting for treatment arm, and baseline scores as a continuous covariate.

9.8.5.5 Safety laboratory analyses

Safety laboratory data will be summarised by treatment arm. Clinically significant abnormalities will be tabulated, and shift tables will be prepared.

9.8.5.6 Adverse events

Adverse events (including SAEs) will be recorded from signing of the ICF until the follow-up visit. Adverse events will be coded using the MedDRA codes.

Adverse events that occur before first treatment with IMP will be listed separately. Treatment emergent AEs will be summarised by PT and SOC, severity and relationship to IMP. Serious Adverse events will also be presented in separate tabulations.

9.8.6 Analysis of pharmacokinetic data

The PK calculations will be based on the PK dataset, and performed by CTC Clinical Trial Consultants, Uppsala, Sweden. The PK parameters will be calculated by Non-Compartmental Analysis using the software Phoenix WinNonlin® version 8.1 or later (Certara, U.S.A.).

In Part A, the following parameters will be estimated from the plasma concentration-time data of golexanolone, if possible:

FULL PROCEDURE:

a. after the first dose: $AUC_{0\text{-}24h}$, C_{max}, T_{max}, $lambda_z$, $T_{1/2}$, Vz/F, Cl/F
b. after the last dose: AUC_{ss}, $C_{max,\ ss}$, $C_{min,\ ss}$, T_{max}, % fluctuation, $lambda_z$, $T_{1/2}$, CL/F, V_z/ F
c. accumulation ratio between the first and the last dose

MODIFIED PROCEDURE:

a. after the first dose: $AUC_{0\text{-}6h}$, $C_{max,}$ T_{max}
b. after the last dose: AUC_{ss}, $C_{max,\ ss}$ and $C_{min,\ ss}$, T_{max}, % fluctuation, lambdaz, $T_{1/2}$, CL/F, Vz/ F

In Part B, C_{trough} will be assessed pre-dose on Days 1, 14, and 28.

The decision to analyse the metabolite profile in human plasma and urine or not will be based on PK results when available. The analysis results will be presented separately from the clinical study report.

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A more detailed description of the PK analyses will be provided in the statistical analysis plan.

9.8.7 Analysis of efficacy parameters

9.8.7.1 PBC-40

Data will be analysed for each domain separately. If data are missing from a domain (typically missed or duplicated answers) the whole domain should be discarded if <50% of items are completed. If >50% of responses are present the median value for the completed items in the domain should be ascribed to the missing items [45].

PBC-40 domain scores will be assumed to be normally distributed [28]. All PBC-40 domain scores will be evaluated within an ANCOVA model accounting for treatment arm, and baseline PBC-40 score as a continuous covariate. Least-square mean differences (95% CIs) between active treatment arms and placebo will be estimated within this ANCOVA framework. In order to preserve the type I error rate a hierarchical closed testing procedure is defined for the cognitive domain, testing first the highest dose, then the mid dose and at the end the smallest dose against placebo. For the other domains P-values will be interpreted descriptively, as measures of the effect size.

9.8.7.2 EQ-5D-3L

Treatment means will be estimated within an ANCOVA model similar to the primary analysis, but P-values will be interpreted descriptively.

9.8.7.3 Epworth Sleepiness Scale

The ESS will be scored based on the appropriate scale documentation with further details to be provided in the statistical analysis plan. Responses to each question and the overall ESS score along with the change from baseline will be summarised using descriptive statistics by visit and treatment arm.

Treatment arms will be compared with respect to significant daytime hypersomnolence, where an overall ESS score will be considered abnormal if the value is ≥10. Results will be tabulated by treatment arm and pairwise comparisons between each of the active treatment arms and placebo will be conducted.

9.8.7.4 Cognitive test battery

Mean and individual change in PHES score from baseline to end of treatment will be summarised by treatment arm. Pairwise comparisons between each of the active treatment arms and placebo will be performed within an ANCOVA model accounting for treatment arm, and baseline overall PHES score as a continuous covariate.

A clinically significant improvement is defined as normalisation of the PHES or individual improvement by more than 2 points [46]. Clinically significant improvement rates will be

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tabulated by treatment arm. Pairwise comparisons between each of the active treatment arms and placebo will be conducted.

Since the PHES was initially designed and validated for more severe hepatic encephalopathy than is typically observed in PBC, the addition of RAVLT and the Category and Letter Fluency tasks from D-KEFS to the PHES to form an expanded battery for PBC will be explored. As part of this exploration, differences between treatment groups on the individual tests will also be explored.

9.8.7.5 Clinical global impression of change

Active and placebo groups will be compared on CGI-C-PBC scores using parametric (ANOVA) methods and methods for binomial variables (*i.e.* responder analysis in which a responder is a subject having a score of 3 or less).

9.8.8 Analysis of exploratory endpoints

The analyses of exploratory endpoints will be specified in the SAP.

9.8.9 Statistical/analytical issues

9.8.9.1 Handling of dropouts or missing data

Procedures for handling of dropouts, missing data and sensitivity analyses will be provided in the statistical analysis plan.

9.8.9.2 Multiple comparison/multiplicity

For the cognitive domain of PBC-40 score a hierarchical closed testing procedure has been defined to preserve the type I error rate. All other P-values will be interpreted descriptively.

9.8.9.3 Interim analyses and data monitoring

An interim analysis for sample size re-assessment will be performed as described in Section 9.8.2. Detailed procedures for the interim analysis will be specified in an interim analysis plan.

9.9 Data Management

Data management based on GCP refers to the activities defined to achieve safe routines to efficiently enter subject information into a database, avoiding errors.

The data management activities, such as procedures of validating data entered in the eCRF, will be described in a separate data management plan. The eCRF will be designed in accordance with the CSP.

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9.9.1 The web based eCRF

Clinical data (including AEs and concomitant medications) will be entered into a 21 CFR Part 11-compliant eCRF (Zelta V2023.3.0.1or higher) provided by Accelsiors. The eCRF includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents, which are to be defined at the site before inclusion of the first subject.

Authorised study site personnel designated by the Investigator will complete data collection. Appropriate training and security measures will be completed with the Investigator and all authorised study site personnel prior to the study being initiated and any data being entered into the system for any study subject.

Captured data will be monitored electronically. Source data verification and source data review will be performed at the site as described in the monitoring guidelines. Any inconsistencies will be presented as;

- automatically generated queries, if triggered by the pre-defined data checks of the eCRF system.
- manually generated queries raised as a result of manual data review by the study team.
- manually generated queries raised by the Monitor as a result of inconsistencies identified during the SDV process.

Queries shall be resolved in a timely manner by a trained member of the site staff.

9.9.2 Entering of data into the eCRF

All data must be entered in English. The eCRFs should always reflect the latest observations made during the subject's participating in the study. Therefore, the eCRFs should be completed as soon as possible during or after the subject's visit.

The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable, or unknown, the Investigator should indicate this in the eCRF. The Investigator will be required to electronically sign off the clinical data.

9.9.3 The query process

The Monitor will review the eCRFs and source documents in order to evaluate them for completeness and consistency. The eCRF will be compared with the respective source documents to ensure that there are no discrepancies between critical data (SDV), in accordance with the monitoring guidelines. All entries, corrections, and alterations are to be made by the Investigator or designee. The Monitor cannot enter data into the eCRFs. Once clinical data have been submitted to the central server via the eCRF, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who

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made the change, together with time and date will be logged. Roles and rights of the site personnel responsible for entering clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible Monitor or Data Manager will raise a query in the EDC application. The appropriate investigational personnel will answer the queries in the eCRF. This will be audit trailed by the EDC application meaning that the name of investigational personnel, time, and date is logged.

The data from the eCRFs will be sent to the Sponsor and a copy will be sent to the study site and filed in the Investigator Study File for archiving after the clinical study report is finalised.

9.9.4 User ID

The eCRF records will be automatically appended with the identification of the creator, by means of their unique UserID. Specified records will be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique UserID and password; date and time stamps will be added automatically at time of electronic signature. If an entry in an eCRF requires change, the correction should be made in accordance with the relevant software procedures.

9.9.5 Audit trail

All changes made to data entered into the eCRF will be fully recorded in a protected audit trail, and a reason for the change will be required.

Once all data have been entered, verified, validated, and signed the database will be locked.

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10 EMERGENCY PROCEDURES

10.1 Emergency contacts

In the case of a medical emergency the Investigator must contact the Medical Monitor at Accelsiors (Table 10.1-1).

Table 10.1-1 Medical emergencies contact

Name	Function in the study	Telephone number and e-mail
PPD	PPD	PPD

10.2 Procedures in case of medical emergency

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. A medical emergency usually constitutes an SAE and is to be reported as such. Detailed SAE reporting procedures are described in Section 9.5.5.7.

10.3 Procedures in case of overdose

An overdose is a dose in excess of the dose specified for each dose level in this CSP.

There are no data on overdosing of golexanolone. There is no known antidote and an overdose in a study subject should be monitored closely and treated symptomatically. Any overdose should be recorded as follows:

- An overdose with associated AE is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF.
- An overdose without associated symptoms is only reported in the subject´s medical records.

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11 STUDY MANAGEMENT

11.1 Changes in the approved clinical study protocol

Any proposed change to the approved final CSP (including appendices) will be documented in a written and numbered CSP amendment. All amendments including substantial changes to the CSP must be approved by the appropriate IEC and/or CA before implementation, according to applicable national regulations, except for changes necessary to eliminate an immediate hazard to study subjects.

A substantial CSP amendment should generally be signed and dated by the same parties who signed the final CSP, as applicable.

11.2 Study timetable

The end of the study is defined as the last visit of the last subject participating in the study. The end of the study will be declared when the last visit of the last subject has been performed and the last human tissue sample collected has been analysed. Analysis of human tissue samples collected will be completed within 2 months from last subject's last visit.

The study is expected to start in Quarter 3, 2022 and to be completed by Quarter 1, 2026.

11.3 Discontinuation of the study

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may also initiate study-site closure, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development.

For site termination:

- Failure of the Investigator to comply with the CSP, the requirements of the IEC or local CA, the Sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
- Total number of participants included earlier than expected.

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If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs, the CAs, and any vendors used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

If the study is halted due to safety reasons or based on the stopping rules detailed in Section 9.3.9.3, the study can only be re-started after regulatory approval via a substantial amendment.

11.4 Final study report and publication of study results

A Clinical Study Report, in compliance with ICH E3; *Structure and content of Clinical Study Reports*, describing the conduct of the study, the statistical analysis performed, and the results obtained, will be prepared by Accelsiors. The report will be reviewed and approved by, as a minimum, the Coordinating Investigator, the Statistician, and the Sponsor.

It is agreed between the Investigator and the Sponsor that data from the study will be used in connection with the development of the IMP. Information about the study may therefore be disclosed by the Sponsor to the Sponsor's scientific advisers and to CAs.

The study results will be reported in the EU clinical trial portal per applicable regulations within 12 months after completion of the study. The Sponsor will report both positive and negative/inconclusive results.

Formal presentation or publication of data collected in this study should be considered as a joint publication by the Investigators and person appointed by the Sponsor. Authorship will be determined by mutual agreement. For multi-centre studies, the first publication should be a joint publication, reporting the combined results from all centres.

If the study duration exceeds one year, the Sponsor must submit an annual safety report to the CA and to the IEC. The report will summarise all SAEs and contain an update of the risk-benefit evaluation if there has been any change since the approval of the clinical study.

The results from this study will be submitted for publication at the discretion of the Sponsor.

11.5 Archiving

The Investigator must arrange for retention at the investigational site of a list of the subjects and their identifying code, subject files, and other study documents.

The Sponsor and the Investigator shall archive the content of the clinical study master file for at least 25 years after the end of the clinical study. The medical files of subjects shall be archived in accordance with national law.

It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

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The Sponsor will archive the Study Master File in accordance with ICH E6 GCP (R2), Section 8 and applicable regulatory requirements.

11.6 Disclosure and confidentiality

All unpublished information concerning the test product and research carried out by the Sponsor, including patent applications, manufacturing processes, basic scientific data, etc., is considered confidential and the sole property of the Sponsor. Disclosure to third parties must be limited to those undertaking legitimate peer review of the scientific and ethical aspects of the study and to those participating, including the recipients of drugs, so that customary medical care and informed consent can be achieved.

11.7 Insurance/indemnity

The Sponsor maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws. The certificate of insurance and an information leaflet containing essential information about the insurance coverage can be provided upon request. The participating subjects are also protected in accordance with national regulations, as applicable.

11.8 Study agreements

The Principal Investigator at the investigational site must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study.

Agreements between Accelsiors and the study sites must be in place before any study-related procedures can take place, or subjects be enrolled.

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13 APPENDICES

13.1 Signature pages

"I agree to the terms of this Clinical Study Protocol."

Sponsor Signatory

PPD

Name

PPD

Signature and date

Sponsor Medical Officer

PPD

Name

PPD

Signature and date

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13.1 Signature pages

Coordinating Investigator

"I agree to the terms of this Clinical Study Protocol. I will conduct the study in accordance with the procedures specified in the protocol, the ethical principles in the latest version of the Declaration of Helsinki, ICH Good Clinical Practice and applicable regulatory requirements".

Signature

PPD

2025-10-03

PPD

Name

Signature and date

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13.1 Signature pages

Principal Investigator

"I agree to the terms of this Clinical Study Protocol. I will conduct the study in accordance with the procedures specified in the protocol, the ethical principles in the latest version of the Declaration of Helsinki, ICH Good Clinical Practice and applicable regulatory requirements".

Signature

Name	*Signature and date*

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13.2 Paris overlap criteria

Clinical Feature	Score
Female gender	+2
ALP:AST ratio	
<1.5	+2
1.5-3.0	0
>3.0	-2
Serum globulin or IgG above normal	
>2.0	+3
1.5-2.0	+2
1.0-1.5	+1
<1.0	0
ANA, SMA, or LKM-1	
>1:80	+3
1:80	+2
1:40	+1
<1:40	0
AMA	
positive	-4
Hepatitis viral markers	
Positive	-3
Negative	+3
Drug history	
Positive	-4
Negative	+1
Average alcohol intake	
<25 g/day	+2
>60 g/day	-2
Liver histology	
Interface hepatitis	+3
Predominante lymphoplasmacytic infiltrate	+1
Rosetting of liver cells	+1
None of the above	-5
Biliary changes	-3
Other changes	-3
Other autoimmune disease	+2
Optional additional parameters	
Seropositivity for other defined autoantibodies	+2
HLA DR3 or DR4	+3
Response to therapy	
Complete	+2
Relapse	+3
Interpretation of aggregate scores:	
Pre-treatment	
Definite AIH	>15
Probable AIH	10-15
Post-treatment	
Definite AIH	>17
Probable AIH	12-17

ALP: Alkaline Phosphatase; AST: Aspartate Transaminase; IgG: Immunoglobulin G; ANA: Anti-nuclear Antibodies; SMA: Smooth Muscle Antibodies; LKM-1: Type 1 Liver-kidney Microsomal antibodies; AMA: Anti-Mitochondrial Antibodies; HLA: Human Leucocyte Antigen