CLINICAL STUDY PROTOCOL

Primary Study Intervention(s)	GSK4532990 Injection
Other Study Intervention(s)	None
Study Identifier	218675
Approval Date	02 Dec 2024
Title	A Phase 2a, single dose, open-label, dose-exploration study to assess the PK-PD activity, safety, and tolerability of GSK4532990 in adult participants with NASH or suspected NASH
Protocol Number	Amendment 3
Compound Number/Name	GSK4532990
Brief Title	Dose Exploration Study of GSK4532990 in Participants with NASH or Suspected NASH
Acronym	SKYLINE (A Phase 2a, **S**ingle dose, open-label, dose-exploration study to assess the P**K** and PD activit**Y**, safety, and tolerabi**L**ity of GSK4532990 **I**n adult participants with **N**ASH or susp**E**cted NASH)
Sponsor	GlaxoSmithKline Research & Development Limited 79 New Oxford Street London WC1A 1DG United Kingdom
Sponsor signatory	Kathy-Ann Cadogan, MBBS Senior Clinical Development Director, Hepatology

Medical monitor name and contact can be found in local study contact information document: Will be provided separately

Based on TMF-14732712 Protocol v3.0.

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PROTOCOL AMENDMENT 3 INVESTIGATOR AGREEMENT

I agree:

- **To conduct the study in compliance with this protocol, any future protocol amendments, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GSK.**
- **To assume responsibility for the proper conduct of the study at this site.**
- **That I am aware of and will comply with GCP and all applicable regulatory requirements.**
- **That I will comply with the terms of the site agreement.**
- **To comply with local bio-safety legislation.**
- **To ensure that all persons assisting me with the study are adequately informed about the GSK study intervention and other study-related duties and functions as described in the protocol.**
- **To supervise any individual or party to whom I have delegated study-related duties and functions conducted at the study site.**
- **To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-related duties and functions.**
- **To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.**
- **To ensure that no clinical samples (including serum samples) are retained on-site or elsewhere without the approval of GSK and the express physical and/or digital informed consent of the participant and/or the participant's LAR.**
- **To perform no biological assays on the clinical samples other than those described in the protocol or its amendment(s).**
- **To co-operate with representative(s) of GSK in the monitoring and data management processes of the study with respect to data entry and resolution of queries about the data.**
- **To have control of all essential documents and records generated under my responsibility before, during, and after the study.**
- **That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator(s)' ownership interest in the sponsor or the study intervention(s), and more generally about their financial ties with the sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.**

Hence, I:

- **Agree to supply GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).**
- **Agree to promptly update this information if any relevant changes occur during the study and for 1 year following completion of the study.**
- **Agree that GSK may disclose any information about such ownership interests and financial ties to regulatory authorities.**
- **Agree to provide GSK with an updated Curriculum Vitae and all other documents required by regulatory agencies for this study.**

Study identifier	218675
Approval date	02 Dec 2024
Title	A Phase 2a, single dose, open-label, dose-exploration study to assess the PK-PD activity, safety, and tolerability of GSK4532990 in adult participants with NASH or suspected NASH
Investigator name	
Signature	
Date of signature (DD Month YYYY)	

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**Document Identifier**
Amendment 3	02 Dec 2024	TMF-20157115
Amendment 2	25 September 2024	TMF-19828475
Amendment 1	01 December 2023	TMF-17419657
Original Protocol	07 September 2023	TMF-16260802

Amendment 3: (02 Dec 2024)

Overall Rationale for the Amendment: This is a global amendment with substantial changes to implement the iDRC's recommendations from Interim Analysis 3 (IA3). In particular, the protocol has been updated to modify the post-dose biopsy from Week 16 to Week 28 and modify the post-dose visits for Treatment Arm 4 (800 mg dose). Revisions to this protocol have been incorporated throughout the document, including changes to the study schema, SoA, updates to the study design, and additional data reviews. There are also points of clarification and formatting corrections throughout the protocol.

LIST OF MAIN CHANGES IN THE PROTOCOL AND THEIR RATIONALE

Section # and Name	Description of Change	Brief Rationale
Title Page	Updated the GSK address.	To comply with GSK template.
Section 1.1 Synopsis Section 3 OBJECTIVES, ENDPOINTS AND ESTIMANDS Section 4.1 Overall Design Section 9.3.3 Secondary Endpoints/Estimands Analyses	Deleted description of conditional outcome of Interim Analysis 3 (IA3).	To clarify that IA3 criterion is met and as a result, study design changes were made.
Section 1.1 Synopsis Section 1.2 Study Schemas Figure 1 and Figure 2 Section 1.3 SoA, Table 3 Section 3 OBJECTIVES, ENDPOINTS AND ESTIMANDS Section 4.1 Overall Design Section 9.3.3 Secondary Endpoints/Estimands Analyses	Updated the study schema with the study visits and aligned other sections for consistency.	To demonstrate schematically the study design change.
Section 1.3 SoA, Table 4	Added study visits between Week 16 through Week 30	New SoA schedule after Week 16 to reflect updated study design

Section # and Name	Description of Change	Brief Rationale
Section 4.1 Overall Design	Deleted the reference of the highest dose not exceeding 800 mg.	To provide clarity that dose may exceed 800 mg if recommended by the DEC and iDRC.
Section 4.4 Criteria for Dose Escalation Decisions	Updated the section to provide clarity on what actions the dose escalation committee may conduct.	To provide clarity on scope of data review for dose escalation to higher doses.
Section 4.6 End-of-Study Definition	Updated the EoS definition.	To align with updated study design.
Section 5.4 Screen Failures	Added “or in discussion with” for screen failure decision the medical monitor.	To provide flexibility.
Section 7.2.1 Participant Addition	Added clarification on sufficient biopsy samples.	To provide clarity and reduce patient burden.
CCI [redacted]		

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
Ae0-24h	Amount of unchanged drug recovered in urine over 0 - 24h post dose
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ASGPR	Asialoglycoprotein receptor
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC%Extrap	Percent of total area under the concentration time curve obtained by extrapolation
AUC0-inf	Area under the concentration-time curve from time zero (pre-dose) to infinity
AUC0-t	Area under the concentration-time curve from time zero (pre-dose) to the last quantifiable concentration
BLN	Baseline average
CAP™	Controlled Attenuation Parameter
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine kinase
CK-18	Cytokeratin 18
CL/F	Apparent clearance
CLR	Renal clearance over a time interval calculated by Ae/AUC at the same time interval (0-24h)
Cmax	Maximum observed serum concentration
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
DBL	Direct bilirubin
DEC	Dose Escalation Committee
DEP	Dose Escalation Plan
DFP	Direct-from-participant
DILI	Drug-induced liver injury
DLT	Dose-limiting toxicity
DTP	Direct-to-participant
ECG	Electrocardiogram
eCRF	Electronic case report form
ELF	Enhanced liver fibrosis
EoS	End-of-study
EW	Early withdrawal
FDA	Food and Drug Administration, United States of America

Abbreviation	Definition
fe0-24h	Percentage of the administrated drug recovered in urine over 0 - 24h post-dose
Fib-4	Fibrosis 4 score
FSFV	First subject first visit
FSH	Follicle stimulating hormone
GalNAc	N-acetylgalactosamine
GCP	Good clinical practices
GGT	Gamma-glutamyl transferase
GLP	Glucagon-like peptide
GSK	GlaxoSmithKline
HbA1c	Glycosylated hemoglobin A1c
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HHS	Home healthcare services
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HRT	Hormonal replacement therapy
HV	Healthy Volunteer
IA	Interim analysis
IB	Investigator's brochure
IC50	Half-maximal inhibitory concentration
ICF	Informed consent form
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICSR	Individual case safety reports
iDRC	Internal Data review committee
IEC	Independent ethics committee
IgM	Immunoglobulin M
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
ISR	Injection site reaction
IVRS	Interactive voice response system
IWRS	Interactive web response system
LAR	Legally acceptable representative
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LLN	Lower limit of normal

Abbreviation	Definition
LMP	Last menstrual period
LOF	Loss-of-function
LSM	Liver stiffness measurement
MedDRA	Medical Dictionary for Regulatory Activities
MRI-PDFF	Magnetic resonance imaging-proton density fat fraction
mRNA	Messenger RNA
MSDS	Material Safety Data Sheet
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NCI	National Cancer Institute
NHV	Normal healthy volunteer
NIH	National Institutes of Health
NIMP	Non-investigational medicinal product
NOAEL	No observed adverse effect level
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic
Pro-C3	Pro-peptide of type III collagen
QTc	Corrected QT
QTcF	QT interval corrected for heart rate according to Fridericia's formula
QTL	Quality tolerance limit
RBP-4	Retinol binding protein-4
RCCS	Randomization and Container Codes Strategy
RNAi	Ribonucleic acid interference
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
siRNA	Small interfering ribonucleic acid
SNP	Single nucleotide polymorphisms
SoA	Schedule of activities
SRT	Safety Review Team
t1/2	Apparent terminal phase half-life
T2DM	Type 2 diabetes mellitus
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
tmax	Time of occurrence of Cmax
UACR	Urine albumin-creatinine ratio
ULN	Upper limit of normal
VCTE™	Vibration-Controlled Transient Elastography

Abbreviation	Definition
VLDL-C	Very low-density lipoprotein cholesterol
Vz/F	Apparent terminal phase volume of distribution
WBC	White blood cell
WOCBP	Woman of childbearing potential
WONCBP	Woman of nonchildbearing potential

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 2a, single dose, open-label, dose-exploration study to assess the PK-PD activity, safety, and tolerability of GSK4532990 in adult participants with NASH or suspected NASH

Brief Title: Dose Exploration Study of GSK4532990 in Participants with NASH or Suspected NASH

Rationale: This is a Phase 2a, single dose, open-label, multi-center, dose exploration study designed to assess the PK and PD activity, safety, and tolerability of GSK4532990 in adult participants with confirmed NASH or suspected NASH (refer to Section 4). This study will further inform the dose exposure-target engagement relationship and potentially inform higher doses or alternate dosing regimen decisions in future clinical development of GSK4532990.

For more details, refer to Section 2.1.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
To assess the effect of a single dose of GSK4532990 on PK-PD target engagement in participants with NASH or suspected NASH	Dual endpoints: • Pre and post dose liver biopsy-derived HSD17B13 protein expression levels • Pre and post dose liver biopsy-derived *HSD17B13* mRNA expression levels
Secondary	
To evaluate GSK4532990 exposure parameters after a single dose in participants with NASH or suspected NASH	Plasma exposure parameters of GSK4532990: • Area under the concentration-time curve from time zero (pre-dose) to the last quantifiable concentration (AUC0-t) • Maximum observed concentration (Cmax)
To evaluate the PD effect of GSK4532990 after a single dose in participants with NASH or suspected NASH	• Percent change from baseline in HSD17B13 protein expression levels at each assigned post-dose biopsy time: Weeks 8, 12, or 28 post-dose • Percent change from baseline in *HSD17B13* mRNA expression levels at each assigned post-dose biopsy time: Weeks 8, 12, or 28 post-dose

Objectives	Endpoints
Safety	
To assess the safety and tolerability of GSK4532990 after a single dose in participants with NASH or suspected NASH	Clinical assessments including: • Occurrence of AEs and SAEs • Change from baseline in vital signs at each visit assessment • Change from baseline in key[a] laboratory measurements at each visit assessment • Occurrence of clinically significant ECG findings at each assessment

[a]Key laboratory measurements are defined in Table 16 Section 10.2.

For more details, refer to Section 3.

Overall Design: The study will include 4 treatment arms, and all participants will receive a single dose of GSK4532990 via SC injection.

Following a screening period of 6 weeks, eligible participants will be assigned into 1 of the 4 treatment arms: 25 mg, 200 mg, 400 mg, or 800 mg. There will be 12 participants allocated to each treatment arm. Each treatment arm will be split into 2 cohorts. The total study duration, including screening procedures, dosing and post-dose follow-up, is approximately 24-36 weeks for each participant (depending on their treatment arm).

All participants will have a liver biopsy performed prior to dosing on Day 1 to collect liver tissue for quantification of baseline hepatic *HSD17B13* mRNA and protein. Participants will be assigned for a second liver biopsy either at 8, 12, or 28 weeks post-dose. Tissue from the second liver biopsy will be used to assess extent of knockdown of hepatic *HSD17B13* mRNA and HSD17B13 protein by GSK4532990 compared to baseline.

After enrollment into Treatment Arms 1-3 (25 mg, 200 mg and 400 mg) has been completed according to Figure 1, enrollment into Treatment Arm 4 (800 mg) will be initiated. The 800 mg Treatment Arm participants will be assigned for a second liver biopsy at 8 weeks or 28 weeks post-dose, respectively (Figure 2).

A fifth treatment arm may be added to the study per recommendation(s) by the DEC and the iDRC. For more details, refer to Section 4.4 and Section 9.4.

Number of Participants: Refer to Section 9.5.

Data Monitoring/Other Committee: Refer to Section 10.1.5.

1.2. Study Schemas

A schematic illustration of the study design is shown in Figure 1 and Figure 2.

Figure 1 Study Schema for Treatment Arms 1-3

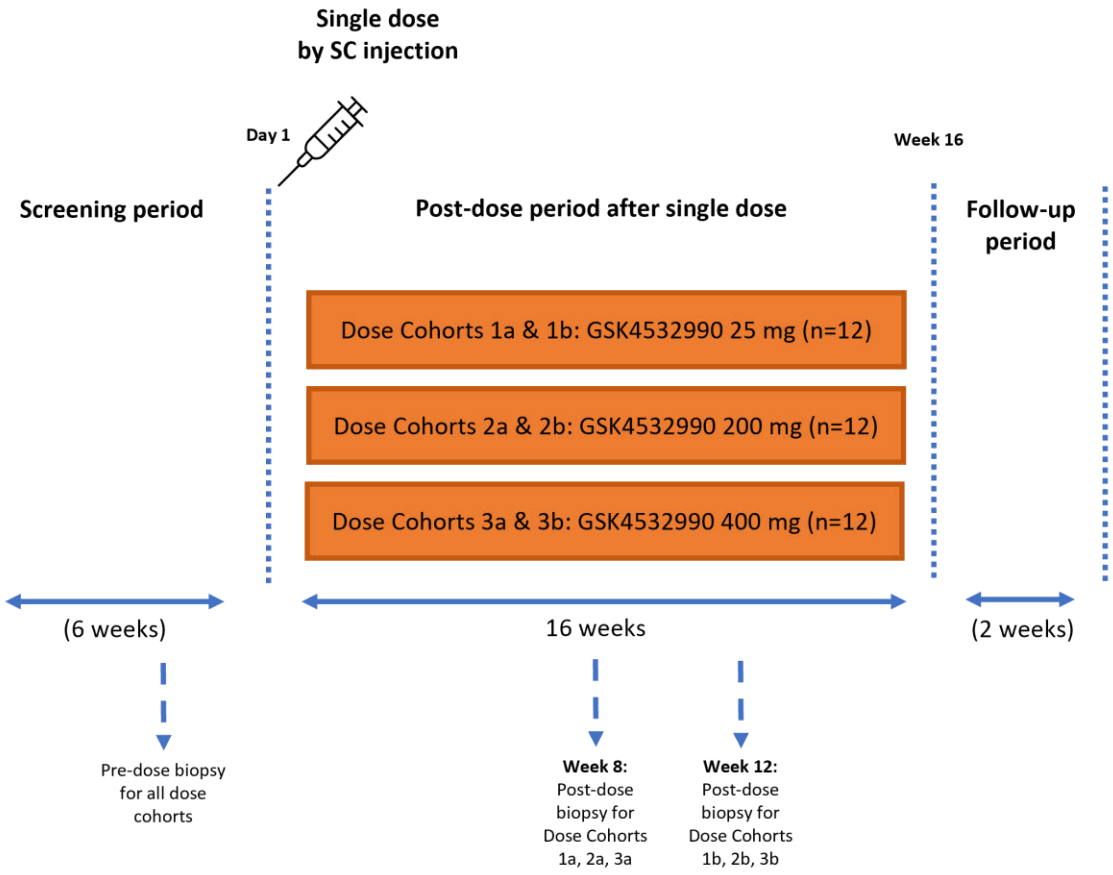
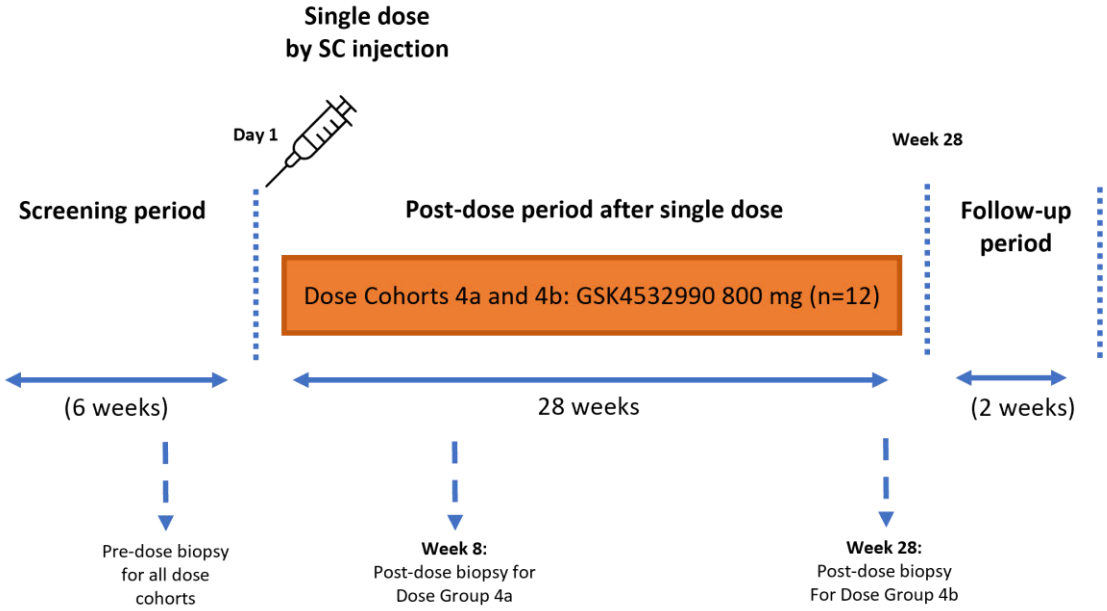


Figure 2 Study Schema for Treatment Arm 4



1.3. Schedule of Activities (SoA)

The Schedules of Activities are presented in the following tables.

Table 1 SoA: Screening

Screening activities have been dispersed across 2 visits to allow early identification of ineligible participants. The goal is to avoid an unnecessary MRI procedure and reduce participant burden.

Visit	Screening 1	Screening 2	Notes
	Week -6	**Week -2**	**The duration and timing of the windows for each Screening visit are relative to Day 1 (dose of study intervention).**
Visit Window	**Week -10 to -4**	**Days -28 to -1**	**Please consider turnaround time of eligibility assessments when scheduling visits.**
General			
Informed consent	X		Refer to Section 10.1.3 for details.
Inclusion and exclusion criteria	X	X	Participants must meet eligibility criteria tested at Screening visit 1 with the exception of genotyping results (Exclusion Criterion #11) prior to proceeding to Screening visit 2. When clinically indicated, assessments (as outlined in the Inclusion and Exclusion Criteria: Section 5.1 and Section 5.2) may be repeated during Screening. When a decision has been made to repeat a test, all the repeated test results supersede the original test results. A test may only be repeated once during Screening. Refer to Section 5.4 for more information on Screen Failures.
Demography and medical history	X		Refer to Section 8.1.1 and Section 8.1.2 for more information.
Prior and concomitant therapy review	X		Refer to Section 6.8 for more information.
Outpatient visit	X	X	
Assessments/Procedures			
Complete physical examination	X		Refer to Section 8.3.1 for more information.
Vital signs	X		Refer to Section 8.3.2 for more information.
12-lead ECG (triplicate)	X		Refer to Section 8.3.3 for more information.
FibroScan®-LSM (VCTE™) and CAP™ (fasting)	X		Refer to Section 8.6.2.1 for more information. Participants must be in a fasted state (no food or drink other than water) for at least 4 hours prior to FibroScan®.

Visit	Screening 1	Screening 2	Notes
	Week -6	**Week -2**	**The duration and timing of the windows for each Screening visit are relative to Day 1 (dose of study intervention).**
Visit Window	**Week -10 to -4**	**Days -28 to -1**	**Please consider turnaround time of eligibility assessments when scheduling visits.**
MRI-PDFF (fasting)		X	Participants should be in a fasted state (no food or drink other than water) for at least 4 hours prior to MRI-PDFF. Please schedule the MRI-PDFF as soon as all Screening 1 eligibility criteria are met with the exception of genotyping results (Exclusion Criterion #11). If MRI-PDFF results are required to confirm eligibility (participants with suspected NASH), please consider the results turnaround time when scheduling subsequent study visits. Refer to Section 8.6.2.2 for more information.
SAE review	X		
Central Laboratory Tests			**Refer to Table 16 in Appendix 2 (Section 10.2).** **Repeat testing during Screening is permitted when clinically indicated. A test may only be repeated once during Screening. Please use the unscheduled/retest visit kit.**
Screening tests (serology, drug screen, FSH)	X		If HCV serology is positive, the HCV RNA result will determine eligibility. FSH is collected for assessment or confirmation of post-menopausal status in female participants (refer to Section 10.4.1 for more information).
Serum pregnancy testing	X		WOCBP only.
Whole blood for genotyping	X		Refer to Section 8.7 for more information
Central clinical chemistry, coagulation, hematology/reticulocyte, urinalysis	X		
HbA1c	X		

Table 2 SoA: Dosing and Intensive PK (Pre-dose and Days 1-3)

Visit	Day 1+											Day 2	Day 3	Notes + Participants should be in a fasted state (no food or drink other than water) prior to this visit.
	Pre-dose	0 m	15 m	30 m	1 hr	2 hr	3 hr	4 hr	6 hr	8 hr	12 hr	24 hr	48 hr	d = day; m = min; hr = hour
Visit Window	d-1 to d1		± 2 m		± 5 m				± 10 m			± 60 m		
General														
Inclusion and exclusion criteria	X													Recheck clinical status before first dose of study intervention. Refer to Section 5.1 and Section 5.2 for Inclusion and Exclusion criteria
Medical history	X													Refer to Section 8.1.2 for more information.
Concomitant therapy review	X													Refer to Section 6.8 for more information.
Treatment assignment	X													
SC dosing		X												
In-house (day/night)	X													Participants may leave the study site after their Day 2 (24 hr post dose) assessment and check back in on Day 3 (48 hr post dose).
Outpatient visit													X	
Assessments/Procedures														
Symptom-driven physical examination	X											X	X	Refer to Section 8.3.1 for more information.
Vital signs and body weight	X											X		Refer to Section 8.3.2 for more information.
12-lead ECG (triplicate)	X				X			X	X	X		X		Refer to Section 8.3.3 for more information. ECGs will be time-matched to the PK sample collection. PK samples should be collected immediately after the time of ECG in order to avoid autonomic changes in heart rate associated with blood sampling.
Liver biopsy and tissue sample handling/analysis (mRNA, protein)	X													Pre-dose biopsy to be completed once all eligibility criteria including (suspected) NASH diagnosis have been confirmed, including results from MRI-PDFF. Refer to Section 8.2.1 for more information.

Visit	Day 1+											Day 2	Day 3	Notes + Participants should be in a fasted state (no food or drink other than water) prior to this visit.
	Pre-dose	0 m	15 m	30 m	1 hr	2 hr	3 hr	4 hr	6 hr	8 hr	12 hr	24 hr	48 hr	d = day; m = min; hr = hour
Visit Window	d-1 to d1		± 2 m		± 5 m				± 10 m			± 60 m		
Alcohol consumption review	X													Refer to Section 5.3.2 Section 8.2.1 for more information.
AE review		X												
SAE review		X												
Injection site reactions review		X												Refer to Section 8.4.4.1.
Central Laboratory Tests														Refer to Table 16 in Appendix 2 (Section 10.2).
Urine pregnancy testing	X													Refer to Section 8.3.5 Test is required for WOCBP, which must be negative prior to administration of study intervention. Participant should be using contraception from the time of Screening Visit 1 and for at least 28 days prior to study intervention.
Central clinical chemistry, coagulation, hematology/reticulocyte, urinalysis (including local urine dipstick test)	X											X	X	Refer to Table 16 in Appendix 2 (Section 10.2).
Fasting lipid profile	X													Participant must be in a fasted state (no food or drink other than water) for at least 10 hours prior to lab tests.
Plasma PK	X (-30 min)		X	X	X	X	X	X	X	X	X	X	X	Pre-dose sample to be taken 30 minutes prior to dosing. Refer to Section 8.5.
Urine PK	spot	Day 1: 0-4 hr, 4-12 hr, 12-24 hr urine collections												Refer to Section 8.5
CCI	[redacted]													
Fasting serum samples for NASH and fibrosis biomarkers	X													Refer to Section 8.6
Urine samples	X													For urine safety biomarkers. Refer to Section 10.7.3

Table 3 SoA: Post-dose Follow-up Period for Treatment Arms 1-3

Visit	W 2 *	W 4+	W 6 *	W 8+	W 12+	W 16+#	W 18$	EW	UNS	Notes: * Visit only required in Cohorts ≥ 400 mg. + Participants should be in a fasted state (no food or drink other than water) for this visit. # EoS visit for everyone except WOCBP $ EoS visit only for WOCBP EoS = end of study, EW = early withdrawal, UNS = unscheduled, W = Week
Visit Window	**±3 d**	**±3 d**	**±3 d**	**±7 d**	**±7 d**	**±7 d**	**±5 d**			**d = Day;**
General										
Concomitant therapy review	X									Refer to Section 6.8 for more information.
Outpatient visit	X	X	X	X	X	X	X	X	X	Except for visits with liver biopsy, assessments may be performed remotely where applicable country and local regulations and infrastructure allow.
Assessments/Procedures										At Week 16: The recommended order of assessments if done on same day: MRI, study visit assessment, biopsy (if applicable)
Symptom-driven physical examination	X	X	X	X	X	X		X	X	Refer to Section 8.3.1 for more information.
Vital signs and body weight		X		X	X	X		X	X	Refer to Section 8.3.2 for more information.
12-lead ECG (triplicate)	X	X	X	X	X	X		X	X	Refer to Section 8.3.3 for more information.
FibroScan®-LSM (VCTE™) and CAP™ (fasting)						X				Refer to Section 8.6.2.1 for more information. Participant must be in a fasted state (no food or drink other than water) for at least 4 hours prior to FibroScan®.
MRI-PDFF (fasting)						X				Refer to Section 8.6.2.2 for more information. Participant should be in a fasted state (no food or drink other than water) for at least 4 hours prior to MRI-PDFF Post-dose MRI may be done on a different day within the visit window range.

Visit	W 2 *	W 4+	W 6 *	W 8+	W 12+	W 16+#	W 18$	EW	UNS	**Notes:** *** Visit only required in Cohorts ≥ 400 mg.** **+ Participants should be in a fasted state (no food or drink other than water) for this visit.** **# EoS visit for everyone except WOCBP** **$ EoS visit only for WOCBP** **EoS = end of study, EW = early withdrawal, UNS = unscheduled, W = Week**
Visit Window	**±3 d**	**±3 d**	**±3 d**	**±7 d**	**±7 d**	**±7 d**	**±5 d**			**d = Day;**
Liver biopsy and tissue sample handling/analysis (mRNA, protein)				X#	X&					#, &: Only applicable to dose cohort biopsy timepoint at W 8, 12, respectively. Post-dose biopsy (W 8 or 12) may be done on different day within the visit window range and after all other assessments if on the same day.
Alcohol consumption review				X	X	X				Refer to Section 5.3.2 for more information.
AE review	X									
SAE review	X									
Central Laboratory Tests										Refer to Table 16 in Appendix 2 (Section 10.2). Repeat testing is permitted when clinically indicated. Please use the unscheduled/retest visit kit.
Urine pregnancy testing							X	X	X	Refer to Section 8.3.5. Test is required for WOCBP.
Central clinical chemistry, coagulation, hematology/reticulocyte, urinalysis (including local urine dipstick test)	X	X	X	X	X	X		X	X	Refer to Table 16 in Appendix 2 (Section 10.2).
Fasting lipid profile		X		X	X	X		X	X	
CCI										
Fasting serum samples for NASH/fibrosis biomarkers					X	X		X	X	Refer to Section 8.6.3
Urine samples		X		X	X	X		X	X	For urine safety biomarkers. Refer to Section 10.7.3.

Table 4 SoA: Post-dose Follow-up Period for Treatment Arm 4

Visit	W 2	W 4+	W 6	W 8+	W 12+	W 16+	W20	W24	W 28+#	W 30$ EoS	EW	UNS	**Notes:** **+ Participants should be in a fasted state (no food or drink other than water) for this visit.** **# EoS visit for everyone except WOCBP** **$ EoS visit only for WOCBP** **EoS = end of study, EW = early withdrawal, UNS = unscheduled, W = Week;**
Visit Window	**±3 d**	**±3 d**	**±3 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±28 d**	**±5 d**			**d = Day**
General													
Concomitant therapy review	X												Refer to Section 6.8 for more information.
Outpatient visit	X	X	X	X	X	X			X	X	X	X	Except for visits with liver biopsy, assessments may be performed remotely where applicable country and local regulations and infrastructure allow.
Phone/remote visit							X	X					
Assessments/Procedures													At Week 28: The recommended order of assessments if done on same day: MRI, study visit assessment, biopsy (if applicable)
Symptom-driven physical examination	X	X	X	X	X	X			X		X	X	Refer to Section 8.3.1 for more information.
Vital signs and body weight		X		X	X	X			X		X	X	Refer to Section 8.3.2 for more information.
12-lead ECG (triplicate)	X	X	X	X	X	X			X		X	X	Refer to Section 8.3.3 for more information.

Visit	W 2	W 4+	W 6	W 8+	W 12+	W 16+	W20	W24	W 28+#	W 30$ EoS	EW	UNS	Notes: + Participants should be in a fasted state (no food or drink other than water) for this visit. # EoS visit for everyone except WOCBP $ EoS visit only for WOCBP EoS = end of study, EW = early withdrawal, UNS = unscheduled, W = Week;
Visit Window	**±3 d**	**±3 d**	**±3 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±28 d**	**±5 d**			**d = Day**
FibroScan®-LSM (VCTE™) and CAP™ (fasting)						X			X				Refer to Section 8.6.2.1 for more information. Participant must be in a fasted state (no food or drink other than water) for at least 4 hours prior to FibroScan®.
MRI-PDFF (fasting)						X			X				Refer to Section 8.6.2.2 for more information. Participant should be in a fasted state (no food or drink other than water) for at least 4 hours prior to MRI-PDFF Post-dose MRI may be done on a different day within the visit window range.
Liver biopsy and tissue sample handling/analysis (mRNA, protein)				X[#]					X[&]				#, &: Only applicable to dose cohort biopsy timepoint at W 8 or 28, respectively. Post-dose biopsy (W 8 or 28) may be done on different day within the visit window range and after all other assessments if on the same day.
Alcohol consumption review				X	X	X	X	X	X				Refer to Section 5.3.2 for more information.

Visit	W 2	W 4+	W 6	W 8+	W 12+	W 16+	W20	W24	W 28+#	W 30$ EoS	EW	UNS	Notes: + Participants should be in a fasted state (no food or drink other than water) for this visit. # EoS visit for everyone except WOCBP $ EoS visit only for WOCBP EoS = end of study, EW = early withdrawal, UNS = unscheduled, W = Week;
Visit Window	**±3 d**	**±3 d**	**±3 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±28 d**	**±5 d**			**d = Day**
AE review									X				
SAE review									X				
Central Laboratory Tests													Refer to Table 16 in Appendix 2 (Section 10.2). Repeat testing is permitted when clinically indicated. Please use the unscheduled/retest visit kit.
Urine pregnancy testing										X	X	X	Refer to Section 8.3.5. Test is required for WOCBP.
Central clinical chemistry, coagulation, hematology/reticulocyte, urinalysis (including local urine dipstick test)	X	X	X	X	X	X			X		X	X	
Fasting lipid profile		X		X	X	X			X		X	X	
CCI													
Fasting serum samples for NASH/fibrosis biomarkers					X	X			X		X	X	Refer to Section 8.6.3
Urine samples		X		X	X	X			X		X	X	For urine safety biomarkers. Refer to Section 10.7.3.

2. INTRODUCTION

2.1. Study Rationale

GSK4532990 is an siRNA-based therapeutic designed to selectively reduce levels of hydroxysteroid 17-β-dehydrogenase-13 (*HSD17B13*) in hepatocytes. The molecule contains a synthetic double-stranded trigger that selectively targets *HSD17B13* mRNA for degradation by the hepatocyte's RNAi machinery, thereby decreasing the amount available for translation. Conjugation with GalNAc provides hepatocyte specific uptake through the ASGPR.

Treatment with GSK4532990 is expected to reduce hepatic production of the HSD17B13 protein and have a similar protective effect on the liver in patients with NASH as seen in individuals harboring enzymatic LOF mutations in HSD17B13 protein.

GSK4532990 is currently under development for the treatment of NASH in a Phase 2b study (218672). In a previous Phase 1/2a study, healthy participants received single ascending doses of 25 mg, 50 mg, 100 mg, or 200 mg subcutaneously on Day 1; confirmed and suspected NASH participants received 25 mg, 100 mg, or 200 mg on Day 1 and Day 29. GSK4532990 was well-tolerated at doses up to 200 mg and demonstrated effective pharmacological response via reduced hepatic *HSD17B13* mRNA and HSD17B13 protein levels on Day 71 post-dose with accompanied reductions of serum biomarkers of liver inflammation (ALT and AST).

This is a Phase 2a, single dose, open-label, multi-center, dose exploration study designed to assess the PK and PD activity, safety, and tolerability of GSK4532990 in adult participants with confirmed NASH or suspected NASH (see Section 4). This study will further inform the dose exposure-target engagement relationship and potentially inform higher doses or alternate dosing regimen decisions in future clinical development of GSK4532990.

2.2. Background

NAFLD is the most common cause of chronic liver disease with a worldwide prevalence of 20% to 30%. NAFLD is strongly associated with features of the metabolic syndrome such as T2DM and obesity [Andrade, 2009; Vernon, 2011; Ekstedt, 2017; Treem, 2021]. NAFLD encompasses a broad spectrum of liver diseases that ranges from simple steatosis to NASH. NASH is the progressive stage of NAFLD whereby hepatocyte inflammation and injury have developed over background steatosis, and it carries a risk for progressive fibrosis, cirrhosis, and end-stage liver disease.

HSD17B13 is a hydroxysteroid dehydrogenase. While its exact physiological function is unclear, it is possibly involved in the metabolism of hormones, fatty acids, and bile acids. In humans, it is primarily expressed in the liver [Liu, 2007]. Hepatic expression is also limited to hepatocytes, with no detectable expression observed in quiescent or activated stellate cells [Ma, 2019]. *HSD17B13* mRNA and HSD17B13 protein expression are higher in livers of mouse models of NAFLD and in humans with NAFLD compared to

non-NAFLD controls [Kampf, 2014; Su, 2014; Ma, 2019; Wang, 2022]. The protein localizes to the surface of lipid droplets as an active dehydrogenase against substrates such as retinol [Ma, 2019], estradiol, and bioactive lipids such as leukotriene B4 [Abul-Husn, 2018], but its physiologically relevant substrate is still unknown.

Human genetic studies identified mutations in HSD17B13 that are protective against development of both alcohol-related and nonalcohol-related liver disease. Among persons with steatosis, the rs72613567:TA variant was also associated with lower odds of NASH (13% for heterozygotes and 52% for homozygotes) and fibrosis (13% for heterozygotes and 61% for homozygotes), as compared with simple steatosis [Abul-Husn, 2018]. Carriers of this variant also have lower plasma ALT and AST levels compared to non-carriers, as well as lower levels of PNPLA3 mRNA expression. Furthermore, this variant confers a reduced risk of liver disease in individuals carrying the disease-associated PNPLA3 rs738409:G risk allele. Importantly, no phenotypic adverse findings have been described in individuals harboring HSD17B13 enzymatic LOF variants. A non-synonymous, enzymatic LOF variant, *HSD17B13* rs62305723:G, has also been reported to protect against chronic liver disease [Ma, 2019].

The properties of these enzymatic LOF HSD17B13 protective variants have inspired therapeutic interest, as they may indicate a role for *HSD17B13* gene silencing in the treatment of liver disease.

GSK4532990 is an siRNA-based therapeutic composed of a synthetic double-stranded oligonucleotide (referred to as an siRNA trigger) designed to selectively target *HSD17B13* mRNA in human hepatocytes. siRNA is a naturally occurring catalytic gene silencing mechanism that is highly specific and efficient [Fire, 1998; Sharp, 2001]. GSK4532990 engages the hepatocyte's siRNA machinery to target *HSD17B13* mRNA for degradation, thereby decreasing the amount of free *HSD17B13* mRNA for translation. GSK4532990 also contains a GalNAc conjugate on the SS that directs selective hepatocyte uptake involving hepatocyte ASGPR.

GSK4532990 was evaluated in a first-in-human single and multiple ascending dose clinical study, AROHSD1001, sponsored by Arrowhead Pharmaceuticals. This study investigated GSK4532990 in adult NHVs and patients with NASH or suspected NASH to evaluate the drug's safety and tolerability, as well as its PK and PD following single or multiple SC doses.

The siRNA trigger in GSK4532990 was designed to specifically target the *HSD17B13* mRNA for degradation in hepatocytes. To promote specific hepatocyte uptake, the siRNA trigger is conjugated on the SS to a GalNAc targeting moiety (NAG789). NAG789 facilitates the hepatocyte uptake of GSK4532990 by endocytosis through the highly expressed, hepatocyte specific ASGPR and was designed to avoid activity against other human microRNA and other non-coding RNA and to avoid acting outside of the liver. Thus, GSK4532990 is not expected to have off-target effects.

GSK4532990 is expected to reduce hepatic production of the HSD17B13 protein and have a similar protective effect as seen in individuals harboring enzymatic LOF mutations of HSD17B13.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of GSK4532990 may be found in the IB.

2.3.1. Risk Assessment

The Sponsor's assessment of known and potential risks of GSK4532990 is summarized in Table 5 .

Table 5 Summary of Potential Risks of Clinical Significance

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study intervention [GSK4532990]		
Injection Site Reactions (ISRs)	ISRs (e.g., pain, erythema, swelling) are anticipated based on similar findings reported in other clinical studies of siRNAs administered subcutaneously. **Preclinical**: Both rat/monkey species had microscopic findings typical for an siRNA. In the monkey, injection sites contained mononuclear cell infiltrates, and in rat there was vacuolation of macrophages/stromal cells and inflammatory cell infiltrates. **Clinical**: ISRs were reported in the Phase 1/2a AROHSD1001 study but only in healthy volunteers. There were no reports of ISRs in the patient cohorts nor amongst any participants receiving placebo. All ISRs reported were mild in intensity and resolved without sequelae. Overall, 5 of 34 (14.7%) HV/patients receiving GSK4532990 reported an AE at the injection site.	ISRs will be graded based on the latest version (Version 5.0) of the CTCAE criteria (see Section 8.4.4.1). Steps will be taken to minimize ISRs such as allowing the GSK4532990 solution to come to room temperature prior to injecting.
Hepatic Events	GSK4532990 targets the liver. siRNA literature has described ALT changes associated with off-target effects of the siRNA seed region on microRNAs in the hepatocyte. The siRNA sequences of the GSK4532990 sense and antisense molecules have been screened for potential mRNA and microRNA homology and sequences with homology were excluded from consideration. Thus, no such off-target effects are anticipated. **Preclinical**: Monkeys and rats had microscopic liver findings typical for an siRNA. In the monkey liver this included cytoplasmic granules in the hepatocytes and/or Kupffer cells. In the rat liver vacuolation/degeneration of hepatocytes, Kupffer cell/macrophage pigment and mononuclear cell	Monitoring rules for liver chemistry (see Section 10.7, Section 10.2). Study screening procedures will include assessment of alcohol and recreational drug use for eligibility determination and enrolled participants will be encouraged to restrict their alcohol consumption to below the eligibility criteria weekly allowance for the duration of study participation. Study screening procedures will include an evaluation of other causes of liver disease, and exclusion of participants with evidence of other liver disease besides

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	infiltrates were noted. Additional rat liver findings included minimal to moderate hyperplasia of oval cells and karyocytomegaly of hepatocytes which were considered adverse at 90 mg/kg/dose based on the severity and additional presence of proliferative changes in the hepatic lobule (increased hepatocyte mitosis). These adverse liver findings set the NOAEL for the chronic rat toxicity study at 30 mg/kg/dose, which is approximately 1.3 and 3.7 times the highest planned clinical exposure by AUC and Cmax, respectively. The PD relevant monkey animal: human safety margin based on the NOAEL of 180 mg/kg, the highest dose tested in the 37-week study, was approximately 20 times human plasma levels achieved at the highest clinical dose of 800 mg based on AUC or Cmax. There is therefore a wide margin of safety between planned clinical doses and animal toxicology study NOAELs. **Clinical**: Adverse changes in transaminases, total bilirubin, or other markers of liver function were not noted as a safety finding in the Phase 1/2a AROHSD1001 study.	NASH. Participants with evidence or a history of cirrhosis will also be excluded.
Reproductive Toxicity	**Preclinical**: Chronic GLP toxicology studies in rat and monkey have been conducted with no toxicologically significant findings in reproductive organs. An embryo-fetal study performed in rat using a surrogate at a high-dose level produced both maternal and embryo-fetal toxicity. Data indicate that GSK4532990 has some pharmacological activity in rabbit and from embryo-fetal development studies in rabbit showed no embryo-fetal toxicity. **Clinical**: No pregnancies reported in HVs/patients receiving active study intervention during the Phase 1/2a study.	Women of child-bearing potential are required to follow appropriate contraceptive guidelines (see Section 10.4). If in the unlikely event a pregnancy does occur, it will be followed to its outcome.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Liver Biopsy	A liver biopsy is commonly part of the standard of care in patients with NASH as well as other adult liver diseases. The risk of bleeding requiring blood transfusion or hospitalization associated with biopsies is 0.04% or less and the risk of less severe but clinically significant events (causing pain, tachycardia, or lower blood pressure) is estimated at 0.2%. Several larger studies show that complications and serious bleeding related to liver biopsy are overwhelmingly more likely in patients with serious clotting disorders, malignancy, and other serious health conditions.	Exclusion of populations at risk of complications and serious bleeding related to liver biopsy including patients with serious clotting disorders, malignancy, and other serious health conditions. Measures of hemostatic function (e.g., platelets, INR) will be conducted prior to biopsy, and may be used to exclude any participant at increased risk for procedural complications. Monitoring and recovery of the participant following the procedure will be consistent with locally accepted standards of clinical practice.
Exposure to high field MRI magnet	MRI can accurately measure the “proton density fat fraction” and will be required to quantify and assess liver fat and is a standardized and objective measurement in NASH trials. Certain metal implants or implantable electronic devices (e.g., pacemakers) are incompatible with MRI scanners	All participants will be screened according to local hospital criteria and trial inclusion/exclusion before entering the MRI room, to ensure they are able to safely have the MRI conducted. Participants who have contraindications to MRI, such as non-MR compatible metal, e.g., implants or implantable electronic devices (e.g., pacemaker) will be excluded from this study.

2.3.2. Benefit Assessment

NASH represents an area of high unmet need with no approved therapies in the United States. This study will therefore contribute to the process of developing GSK4532990 for the potential treatment of NASH. Medical evaluations associated with this study include a medical history and a physical examination, in addition to a variety of blood and imaging tests. Importantly, the participants will undergo a liver biopsy before and after treatment since assessing *HSD17B13* knockdown in the liver is the primary objective of this study. However, the risk of complications from liver biopsy is low [Rockey, 2009].

While it is not anticipated that there would be therapeutic benefit from this single dose study, individual participants in the study may benefit in the short-term from more intensive and frequent medical care as reflected by the SoA, which is more than typical standard of care for this targeted population of participants with NASH or suspected NASH.

The assessment of known and potential risks as well as the proposed mitigation strategy is summarized in Table 5. In an effort to better understand the safety profile of GSK4532990 and identify any further risks, additional monitoring criteria are presented in Section 10.7.

2.3.3. Overall Benefit-Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with GSK4532990 are justified by the anticipated benefits that may be afforded to participants with NASH or suspected NASH.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

The study objectives and endpoints are presented in Table 6.

Table 6 Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the effect of a single dose of GSK4532990 on PK-PD target engagement in participants with NASH or suspected NASH	Dual endpoints: • Pre and post dose liver biopsy-derived HSD17B13 protein expression levels • Pre and post dose liver biopsy-derived *HSD17B13* mRNA expression levels
Secondary	
To evaluate GSK4532990 exposure parameters after a single dose in participants with NASH or suspected NASH	Plasma exposure parameters of GSK4532990: • Area under the concentration-time curve from time zero (pre-dose) to the last quantifiable concentration (AUC0-t) • Maximum observed concentration (Cmax)

Objectives	Endpoints
To evaluate the PD effect of GSK4532990 after a single dose in participants with NASH or suspected NASH	• Percent change from baseline in the observed HSD17B13 protein expression levels at each assigned post-dose biopsy time: Weeks 8, 12, or 28 post-dose • Percent change from baseline in the observed *HSD17B13* mRNA expression levels at each assigned post-dose biopsy time: Weeks 8, 12, or 28 post-dose
Safety	
To assess the safety and tolerability of GSK4532990 after a single dose in participants with NASH or suspected NASH	Clinical assessments including: • Occurrence of AEs and SAEs • Change from baseline in vital signs at each visit assessment • Change from baseline in key[a] laboratory measurements at each visit assessment • Occurrence of clinically significant ECG findings at each assessment
Exploratory	
CCI [redacted]	

[a]Key laboratory measurements are defined in Table 16, Section 10.2.

Primary Objective Estimands

The primary clinical questions of interest for the primary objective are:

- What is the predicted mean percent change from baseline of HSD17B13 protein levels, derived from the PK-PD target engagement model at each treatment arm in adult participants with proven or suspected NASH treated with GSK4532990 regardless of prohibited medication, increase in self-reported alcohol consumption, or delays in post-dose biopsy times?
- What is the predicted mean percent change from baseline of *HSD17B13* mRNA levels, derived from the PK-PD target engagement model at each treatment arm in adult participants with proven or suspected NASH treated with GSK4532990 regardless of prohibited medication, increase in self-reported alcohol consumption, or delays in post-dose biopsy times?

Additional clinical questions of interest for the primary objective are as above but up until the use of prohibited medication or before any increase in self-reported alcohol consumption as defined in Section 5.2 and Section 5.3.2.

The estimands are described by the following attributes:

	Primary estimands	**Additional Estimands**
Treatment	GSK4532990 – doses: 25, 200, 400 and 800 mg	
Population	Adult participants with proven or suspected NASH	
Variables (dual endpoints)	Pre and post dose liver biopsy-derived HSD17B13 protein expression levels Pre and post dose liver biopsy-derived *HSD17B13* mRNA expression levels	
Population-level summary measure	Predicted mean and 95% CI of percent change from baseline of HSD17B13 protein derived from the PK-PD target engagement model at each treatment arm and post-dose biopsy time Predicted mean and 95% CI of percent change from baseline of *HSD17B13* mRNA derived from the PK-PD target engagement model at each treatment arm and post-dose biopsy time	
Intercurrent Events & Strategy	Use of prohibited medication: addressed with "Treatment policy" strategy (i.e., use available data regardless of use of prohibited medication) Increase in self-reported alcohol consumption which exceeds eligibility criteria as defined in Section 5.2 and Section 5.3.2: addressed with "Treatment policy" strategy (i.e., use available data regardless of increased alcohol consumption) Delays in post-dose biopsy times for any reason: addressed with "Treatment policy" strategy (i.e., data will be used even if the biopsy was outside the time window)	Use of prohibited medication: addressed with "Whilst not on prohibited medication" strategy (i.e., use available data up until the use of prohibited medication) Increase in self-reported alcohol consumption which exceeds eligibility criteria as defined in Section 5.2 and Section 5.3.2: addressed with "Whilst not exceeding the weekly limit of alcohol" strategy (i.e., use available data up until the week of increased alcohol consumption) Delays in post-dose biopsy times for any reason: addressed with "Treatment policy" strategy (i.e., data will be used even if the biopsy was outside the time window)

Rationale for primary estimand: It is of interest to estimate the mean and 95% CI of percent change from baseline based on the PK-PD target engagement model regardless of the use of prohibited medication or increased self-reported alcohol consumption to reflect the real-world setting.

Rationale for additional estimand: It is of interest to estimate the mean and 95% CI of percent change from baseline based on the PK-PD target engagement model up until the use of prohibited medication and/or increased alcohol consumption which may influence the PK-PD target engagement model parameter estimates.

Secondary Objective Estimands

The secondary and safety study objectives will be assessed using the endpoints defined in Section 3. They share the same estimand elements of intervention, population, intercurrent events and strategies as the primary estimands. Population-level summary measures are provided in Table 7.

Table 7 Summary Measures

Endpoint	Population-level Summary Measure
Secondary	
• Percent change from baseline in HSD17B13 protein expression levels at each post-dose biopsy time: Weeks 8, 12, 28, post-dose • Percent change from baseline in *HSD17B13* mRNA expression levels at each post-dose biopsy time: Weeks 8, 12, 28 post-dose	Mean percentage change from baseline to post-dose biopsy for each treatment arm
Exposure parameters • Area under the concentration-time curve from time zero (pre-dose) to the last quantifiable concentration (AUC0-t) • Maximum observed concentration (Cmax)	Means or geometric means (where applicable) for each treatment arm
Safety	
• Occurrence of AEs and SAEs from administration of study intervention to EoS. • Change from baseline in vital signs at each visit assessment. • Change from baseline in laboratory measurements at each visit assessment. • Occurrence of clinically significant ECG findings at each visit assessment.	AE data, clinically important vital sign and key laboratory data, and clinically significant ECG data will be summarized using counts, frequencies and percentages. The vital sign and key laboratory data will also be summarized using mean and median as appropriate depending on the distribution of each variable.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2a, single dose, open-label, multi-center, dose-exploration study designed to assess the PK and PD activity, safety, and tolerability of GSK4532990 in adult participants with NASH or suspected NASH. The study will include 4 treatment arms (with the possibility of 5 total treatment arms, depending on recommendations by the DEC and iDRC – see below), all receiving a single dose of GSK4532990 via SC injection.

Following a screening period of 6 weeks, it is planned that eligible participants will be assigned into 1 of the 4 treatment arms: 25 mg, 200 mg, 400 mg or 800 mg. There will be approximately 12 participants allocated to each treatment arm, for a total of 48 participants planned across 4 treatment arms. Each treatment arm will be split into 2 dose

cohorts. Approximately 6 participants will be enrolled in each dose cohort. Participants will be randomized to dose cohorts, where feasible (Figure 3). The total study duration, including screening procedures, dosing and post-dose follow-up for each participant, is approximately 24 weeks for Treatment Arms 1-3 and 36 weeks for Treatment Arm 4 (Figure 3).

All participants will have a liver biopsy performed prior to dosing on Day 1 to collect liver tissue for quantification of baseline hepatic *HSD17B13* mRNA and protein. In Dose Cohorts 1a, 2a, 3a, and 4a (25 mg, 200 mg, 400 mg, and 800 mg respectively), participants will be assigned for a second liver biopsy 8 weeks post-dose, while participants in Dose Cohorts 1b, 2b, and 3b (25 mg, 200 mg and 400 mg respectively) will have a liver biopsy performed 12 weeks and Dose Cohort 4b (800 mg) will have a liver biopsy performed at 28 weeks post-dose, as outlined in Table 3 and Table 4 SoA, respectively.

After enrollment into the 25 mg, 200 mg, and 400 mg Treatment Arms has been completed according to Figure 3, enrollment into the 800 mg Treatment Arm will be initiated. The 800 mg Treatment Arm will be comprised of Dose Cohorts 4a and 4b and participants will be assigned for a second liver biopsy 8 weeks and 28 weeks post-dose, respectively (Figure 2).

As per the iDRC recommendation at IA3, the post-dose biopsy for Dose Cohort 4b has moved from Week 16 (the original post-dose biopsy timepoint) to Week 28. Participants already assigned to Dose Cohort 4b (or Dose Cohort 4c in PA02) prior to the IA3 recommendation, upon reconsent, will follow the updated study design as outlined in the Table 4 SoA. All newly enrolled Dose Cohort 4b participants will have a liver biopsy performed 28 weeks post-dose. Dose Cohort 4a will also follow the Table 4 SoA.

Tissue from the second liver biopsy will be used to assess extent of knockdown of hepatic *HSD17B13* mRNA and HSD17B13 protein by GSK4532990 compared to baseline.

A fifth treatment arm may be added to the study if an intermediate or higher dose is recommended by the DEC and iDRC (see Section 4.4) Details regarding this potential fifth treatment arm are provided in the iDRC Charter will be implemented through another protocol and SAP amendment, if applicable.

If a fifth treatment arm is added, the potential total number of participants for this study is approximately 60 (n= up to 12 participants/treatment arm).

For doses 400 mg and above:

Sentinel dosing will be employed for the first participant of each treatment arm, starting from 400 mg and above. The sentinel participant will be dosed in advance of the rest of the participants in their respective treatment arm. The sentinel participant will be observed for approximately 3 days post-dose, with the first 24 hours confined at the clinical site. The participant may be discharged on Day 2 and will return to the clinical site for outpatient visits per the SoA (Section 1.3). Upon review of the safety data

collected through Day 3, the remaining participants in the respective treatment arm may be enrolled as outlined in the DEP.

GSK4532990 is rapidly cleared in plasma with a half-life of approximately 4 hours. An observation period of 3 days is considered sufficient duration for clearance of higher dosing in this study. If it is deemed necessary, following review of the data from sentinel dosing of a participant, sentinel dosing of an additional participant may be required.

Safety and PK data will be reviewed when 6 participants in a treatment arm reach Day 75 and assessed by the DEC prior to progression to the next dose escalation, if recommended (see Section 4.4). Additional details regarding the remit, participants, and conduct of the DEC will be outlined in the DEP.

Figure 3 Study Enrollment Schema and Associated Data Reviews

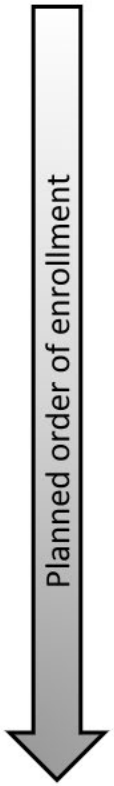
Figure 3A:

Enrollment into the dose cohorts through to Treatment Arm 4 (800 mg) sentinel participant is outlined below. Once a schedule has been enrolled, the next commences. Rationale for the order of the dose cohorts and number of participants assigned to each schedule is due to prioritized timing of specific data for internal development planning and decision-making and optimization of timing for study enrollment and completion.

Figure 3B:

The table outlines the coordinated data review and the approximate number of participants from a given dose cohort included in the data review upon completion of the associated schedules outlined in Figure 3A. Sentinel reviews will be conducted by the DEC while interim analyses will be conducted by the iDRC.

A



Schedule	Dose Cohort (n = # participants per schedule)
1	Sentinel participant for Dose Cohort 3a (n=1)
2	Randomize to Dose Cohort 2a (n=3) or Dose Cohort 3a (n=2)
3	Randomize to Dose Cohort 2b (n=3) or Dose Cohort 3b (n=3)
4	Dose Cohort 1b (n=3)
5	Dose Cohort 1a (n=3)
6	Randomize to Dose Cohort 1b (n=3), Dose Cohort 2b (n=3) or Dose Cohort 3b (n=3)
7	Randomize to Dose Cohort 1a (n=3), Dose Cohort 2a (n=3) or Dose Cohort 3a (n=3)
8	Sentinel participant for Treatment Arm 4 (800 mg)
9	Enroll remaining Treatment Arm 4 (n=11)

B

Dose Cohort	Cohort 1a	Cohort 1b	Cohort 2a	Cohort 2b	Cohort 3a	Cohort 3b	Cohort 4a	Cohort 4b
Dose	25 mg		200 mg		400 mg		800 mg	
Post-dose Biopsy Timepoint	Week 8	Week 12	Week 8	Week 12	Week 8	Week 12	Week 8	Week 28
Review Type	**# of Participants**							
Sentinel Review 1					1			
Interim Analysis 1			3		3			
Dose Escalation Review (400 mg) and Interim Analysis 2			3	3	3	3		
Interim Analysis 3	3	3	3	3	3	3		
Sentinel Review 2								1
Dose Escalation Review (800 mg) and Interim Analysis 4	Refer to Section 4.4 and Section 9.4, Table 15							

4.2. Scientific Rationale for Study Design

GSK4532990 is currently under development for the treatment of NASH in a Phase 2b study (218672). GSK4532990 is well-tolerated at doses up to 200 mg and demonstrated effective pharmacological response via reduced hepatic *HSD17B13* mRNA and HSD17B13 protein levels.

As a non-invasive biomarker for target engagement is not available to facilitate dose selection, in this study, liver biopsies at baseline and after dosing are required to measure the effect of GSK4532990 on *HSD17B13* gene and protein expression. This study will measure baseline hepatic *HSD17B13* mRNA and protein levels and post-dose levels at multiple time points after a single dose of GSK4532990, ranging from 25 mg up to 800 mg (Figure 4). The outcome of this study will enable characterization of the dose-exposure-target engagement relationship as it pertains to the extent and duration of hepatic HSD17B13 knockdown and investigate correlations with other non-invasive tests utilized in NASH trials CCI [redacted]

The patient population selected for this study includes those who may ultimately benefit from GSK4532990. To that end, while it is not anticipated that this patient population is enriched for carriers of the *HSD17B13* rs72613567 TA variant since carriers have reduced risk of liver disease, this study excludes homozygous TA/TA carriers of this variant to limit potentially confounding data.

Finally, as doses of 400 mg and higher have not yet been investigated in a patient population before, safety considerations and mitigation steps have been put into place in this study, such as sentinel dosing and including a DEC to recommend dose escalation decisions, as outlined in Section 4.4 and the DEP.

4.2.1. Input from Individuals Representative of the Study Population

Insights from the same patient population informing the prior Phase 2 study (218672), and information within the NASH Externally Led Patient-Focused Drug Development Report by the Global Liver Institute (Meeting 4 Nov 2021, report 7 March 2022) were reviewed during the design of this protocol.

The relevant patient insights informing the design and implementation of this study is maintained in the Trial Master File.

It is GSK's intent to continually engage patients which may influence future study designs for this disease area and aim to improve the patient experience within clinical research.

4.3. Justification for Dose

The goal of this study is to characterize the target engagement of GSK4532990 on hepatic *HSD17B13* knockdown over time following single SC administration of ascending doses. The doses of GSK4532990 to be included in this study are based on the observed safety and PK/PD modeling of a previously conducted Phase 1/2a study (AROHSD1001) data.

In AROHSD1001, healthy participants received single escalating doses of 25 mg, 50 mg, 100 mg, or 200 mg SC on Day 1, and confirmed or suspected NASH participants received 25 mg, 100 mg, or 200 mg on Day 1 and Day 29. GSK4532990 was well tolerated in both NHVs and participants with confirmed or suspected NASH, with no serious AEs, no AE-related study or drug discontinuations, no DLTs, or deaths.

Hepatic *HSD17B13* mRNA and protein levels, GSK4532990 PK, and serum ALT data were obtained from the NHV and NASH participants who received SC doses of 25 mg to 200 mg. A population PK/PD model was developed and can successfully predict the reduction in ALT over 113 days post-dose and hepatic HSD17B13 protein up to 71 days post-dose following a single or two SC injections of up to 200 mg GSK4532990.

A study with a broader dose range is required to better understand the extent and duration of GSK4532990 target engagement (hepatic HSD17B13 protein and mRNA knockdown). A wide range of doses (25 mg, 200 mg, 400 mg, and 800 mg) was selected based on the aforementioned PK/PD model of change in HSD17B13 protein observed in AROHSD1001 to investigate maximum target engagement and duration of inhibition of hepatic HSD17B13 translation. A placebo group is not necessary as the objective of the study is to measure the change in HSD17B13 protein and mRNA after administration of study intervention in addition to reduce patient burden, feasibility concerns and as it relates to internal development planning. The lowest dose of 25 mg was selected given the minimal effect observed in the AROHSD1001 study, which will help inform the lower portion of the exposure-response curve.

Anticipated Exposure and Safety Multiples for the Selected Dose Range

CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted] Additional information about these studies can be found in the IB, Section 4.4 .

Furthermore, these are planned doses with the assumption of linear PK at doses greater than the 200 mg evaluated in AROHSD1001, meaning if saturation is observed at the higher doses, the likelihood of achieving NOAEL exposures may also be reduced/modulated. The specific doses in this study are subject to change based upon emerging PK, PD, and safety data gathered in this study.

CCI

[redacted]

4.4. Criteria for Dose Escalation Decisions

This study will utilize a DEC to evaluate data prior to escalating to doses above 400 mg. Dose escalation will proceed according to the study design until the highest planned dose cohort is completed, unless the trial is stopped early by the Sponsor per recommendations by the DEC. Dose escalation above 400 mg will require approval by the DEC based on evaluation of all available safety data including but not limited to AEs, vital signs, laboratory findings, ECG parameters, and any available PK data. The DEC will meet when data are available from a minimum of 6 dosed participants in a treatment arm, from dosing (Day 1) through to Day 75. The actual subsequent dose(s) after 400 mg to be administered may be adjusted based on safety, and where available, PK data per recommendation by the DEC. The DEC recommendations may include, but are not limited to, the following actions:

- Stopping at the 400 mg or 800 mg dose tested,
- Testing 600 mg first as an intermediate dose before dose escalating to 800 mg (and as a result, adding a treatment arm),
- Dose escalating to 800 mg
- Dose escalation to doses greater than 800 mg (and as a result, potentially adding a treatment arm)
    - If the DEC allows this dose escalation, the selection of the higher dose will be determined by the iDRC – refer to Section 9.4, or
- De-escalating from 800 mg or a higher dose to an intermediate dose (e.g. 600 mg).

Additional details regarding the remit, participants, and conduct of the DEC and iDRC will be outlined in the DEP and the iDRC Charter, respectively.

4.5. Stopping Criteria for Dose Escalation

Progression to the next higher dose level after 400 mg will be halted if any of the criteria detailed in Table 9, are met. The dose escalation will stop, and no further participants will be dosed at that dose level or any higher level; however, dosing at the lower dose levels may occur.

Table 9 Stopping Criteria for Dose Escalation

General (These criteria apply only to treatment arms ≥400 mg)	• Any participant in a treatment arm experiences a serious adverse reaction (i.e. an SAE considered at least possibly related to the administration of GSK4532990). • Two or more participants in a treatment arm experience the same adverse event of CTCAE Grade 3 or above that can be reasonably attributed to dosing with GSK4532990. • Three or more participants in a treatment arm experience the same adverse event of CTCAE Grade 2 or above that can be reasonably attributed to dosing with GSK4532990.
Liver	Two or more participants at any dose have suspected liver failure where all of the following criteria are met. • One of the following, whichever comes first ○ ALT[a] ≥x3 ULN ○ AST[a] ≥x3 ULN ○ ALP ≥x3 ULN ○ ALT[b] ≥2x participant's BLN ALT ○ AST[b] ≥2x participant's BLN AST ○ ALT ≥300 U/L ○ AST ≥300 U/L ○ ALP ≥300 U/L • TBL ≥2x ULN (≥35% direct bilirubin) • INR ≥1.5 • Absence of other credible etiology
Renal	Increase from baseline creatinine ≥0.5 mg/dL or urine albumin/creatinine ratio ≥500 mg/g and ≥2x baseline. In the absence of other credible etiology
Other	ISR ≥ CTCAE Grade 3
PK	2 or more participants in a treatment arm reach monkey NOAEL by one of the following: • AUC(0-24h) ≥697,000 ng*h/mL • Cmax ≥41,800 ng/mL

a. If participant's baseline average ALT or AST is within normal limits
b. If participant's baseline average ALT or AST is elevated (>ULN)

4.6. End-of-Study Definition

A participant is considered to have completed the study if they have completed all periods of the study, including the EoS visit. The end of the study is defined as the date of the last visit of the last participant in the study.

- Week 16 (or Week 28 for Treatment Arm 4 participants) is EoS for all participants except WOCBP.
- Week 18 (or Week 30 for Treatment Arm 4 participants) is EoS for WOCBP.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

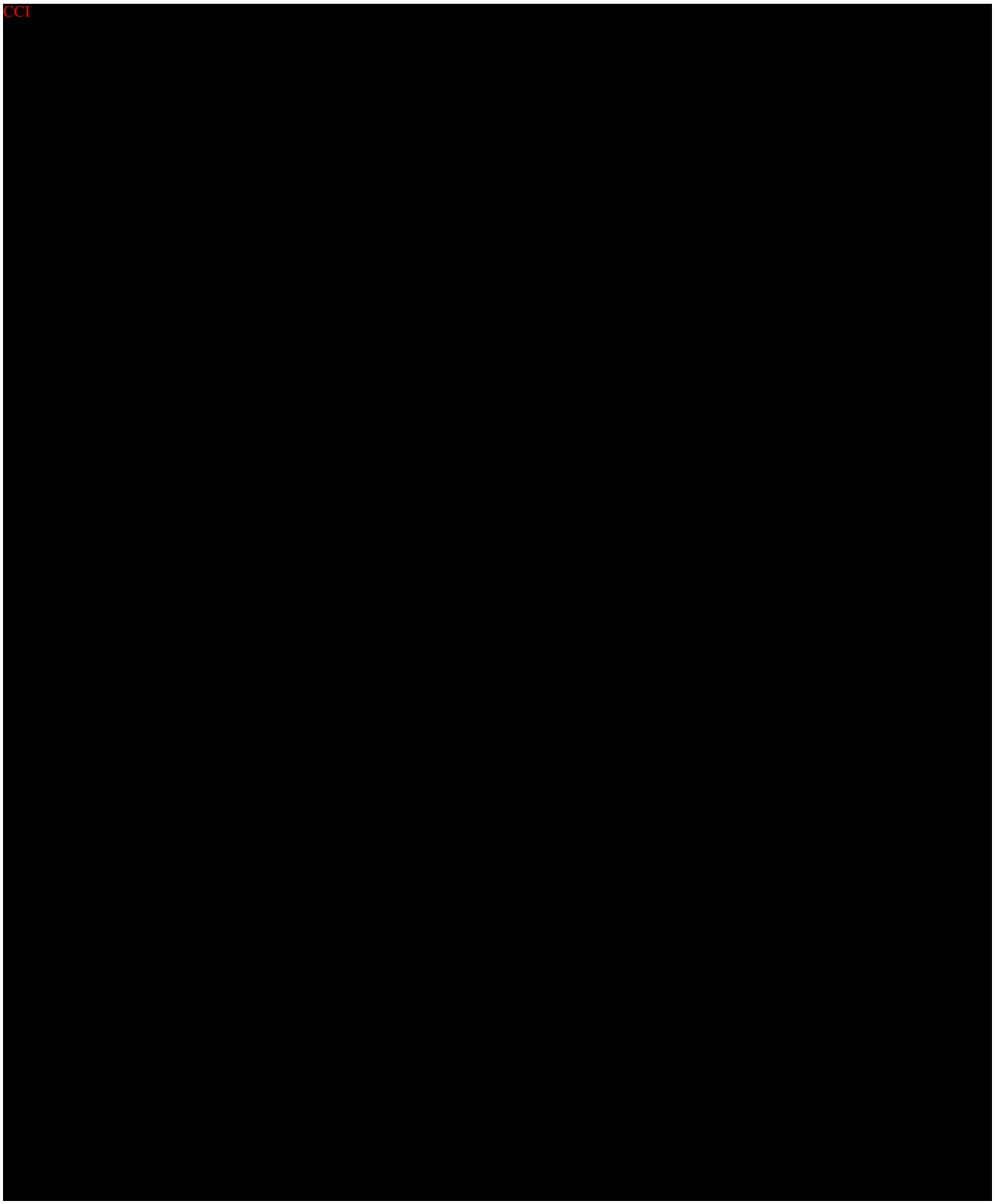
Participants are eligible to be included in the study only if all following criteria apply:

1. Participant must be 18 to 75 years of age inclusive, at the time of screening.
2. Participant must be capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
3. Participants who have proven diagnosis of NASH **or** suspected NASH demonstrated by the following:

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[redacted]

CCI



5.2. Exclusion Criteria

Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:

1. Cirrhosis or current unstable liver or biliary disease [redacted]
2. Other causes of liver disease including, but not limited to, alcohol-related liver disease, autoimmune disorders [redacted]
3. [redacted]
4.
5.
6.
7.
8.
9.
10.
11.
12.
13.
14.

15. CCI [redacted]
16. Known weight loss of ≥5% within 3 months prior to Screening 1.
17. Weight reduction surgery or procedures CCI [redacted] CCI [redacted] within 2 years of Screening 1 and/or planned during the study.
18. CCI [redacted]
19. [redacted]
20. [redacted]
21. Any contraindication to undergoing liver biopsy CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted]
22. Any contraindication to undergoing Magnetic Resonance Imaging or FibroScan®.
23. CCI [redacted]
24. [redacted]
25. [redacted]
26. [redacted]
27. [redacted]
28. [redacted]

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

There are no meal or dietary restrictions except for the visits when fasting is required. Participants will be encouraged to maintain healthy eating habits during the conduct of the study.

5.3.2. Alcohol Consumption

Self-reported average alcohol consumption will be recorded as per SoA (Section 1.3), and participants will be encouraged to remain below the eligibility criteria of <21 standard drinks per week (males) or <14 standard drinks per week (females).

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently entered into the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes but is not limited to: demography, screen failure details, eligibility criteria, any protocol deviations, and any SAEs.

Retesting when clinically indicated (e.g., spurious results or sample handling error), as determined by the investigator, designee/sub-investigator and/or in discussion with the GSK medical monitor, during the screening period is allowed. If the laboratory or FibroScan® criteria are not met, the test may be repeated once within the screening period without this constituting a rescreen. If the laboratory or FibroScan® criteria are not met for a second time, they will be considered a screen failure.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once if there is reasonable possibility that the individual would be eligible, in the opinion of the investigator and/or in discussion with the GSK medical monitor. Rescreened participants should be assigned a new participant number for every screening/rescreening event.

5.5. Criteria for Temporarily Delaying Administration of Study Intervention

Not applicable for this single dose study.

6. STUDY INTERVENTIONS AND CONCOMITANT THERAPY

The definition of study intervention is provided in the table of definitions.

6.1. Study Intervention Administered

Study intervention is presented in Table 10.

Table 10 Study Intervention Administered

Injection Name	GSK4532990
Type	Drug
Dose Formulation	Solution for Injection
Unit Dose Strengths	CCI [redacted]
Route of Administration	SC injection
Use	Experimental
IMP and NIMP	IMP
Sourcing	Provided centrally by the Sponsor or designee
Packaging and Labelling	Study intervention will be provided in a single-use vial. Each single-use vial will be labelled as required per country requirement.

Table 11 Study Arm(s)

Arm Title	GSK4532990 25 mg	GSK4532990 200 mg	GSK4532990 400 mg	GSK4532990 800 mg
Arm Type	Experimental	Experimental	Experimental	Experimental
Arm Description	Single dose of CCI [redacted] of GSK4532990 CCI [redacted]	Single dose of CCI [redacted] of GSK4532990 CCI [redacted]	Single dose of CCI [redacted] of GSK4532990 CCI [redacted]	Single dose of CCI [redacted] of GSK4532990 CCI [redacted]

6.2. Preparation, Handling, Storage, and Accountability

The investigator or designee must confirm appropriate conditions (e.g., temperature) have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention. If allowed by country regulation/ethics, study intervention may be administered by a HHS professional.

All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, the head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy manual.

Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff.

A MSDS/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

0.9% normal saline, if used for study intervention dilution, will not be supplied by the Sponsor. It will be purchased commercially by the study site, subsidiary, or designee and used in its commercial container closure system as single dose product. The manufacture's drug label instructions and/or packet insert should be followed for handling, dose preparation, and administration. Sites should use the most up to date version of packet insert.

6.3. Assignment to Study Intervention

Type of Study	Open-label
Study using IVRS/IWRS	All participants will be centrally assigned or randomized (where applicable) to study intervention using an IVRS/IWRS as outlined in Figure 3A. Study intervention will be dispensed on Day 1 as summarized in the SoA.
Study using pre-coded randomization provided to site	On Day 1, participants will be assigned a unique number in ascending numerical order at each study site. The assigned number encodes the participant's assignment to one of the dose cohorts in Schedules 2, 3, 6 or 7, according to the enrollment schedule (Figure 3) generated prior to the study by the statistics department at GSK.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of the dose administered in the clinic will be recorded in the source documents.

A record of the quantity of GSK4532990 dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records.

6.5. Dose modification

Not applicable for this single dose study.

6.6. Continued Access to Study Intervention After the End of the Study

No study interventions will be offered after the end of study, unless approved by the Sponsor.

6.7. Treatment of Overdose

An overdose is any dose of GSK4532990 given to a participant that exceeds the planned dose for an individual within a given dose group.

In the event of an overdose, the investigator or designee should:

- Closely monitor the participant for any AE/SAE and laboratory abnormalities until Day 120 as the anticipated PD effect is significant longer than the PK half-life (approximately 4 hours), as medically appropriate.
- Document the quantity of the excess dose in the eCRF.

6.8. Prior and Concomitant Therapy

Concomitant care may be given as medically indicated. Participants must abstain from taking any new class of the medications or investigational drugs listed in Section 5.1 (Inclusion Criteria) during the study.

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Not applicable for this study.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).
- A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.
- Investigators will attempt to contact participants who do not return for scheduled visits or follow-up.
- At the time of discontinuing from the study, if possible, an EW visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

- The participant will be permanently discontinued from the study at that time. Withdrawn participants cannot subsequently re-enter the study.
- All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analyses. If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- The primary reason for participant discontinuation/ withdrawal from the study will be documented in the eCRF based on the list below:
- Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved (see Section 10.3.5.7).

7.2.1. Participant Addition

In the event that one or more participants within a dose cohort withdraws prior to the pre- or post-dose biopsy or a biopsy sample is not evaluable, additional participants with a unique study ID may be enrolled. This will ensure that a given treatment arm has a sufficient number of participants with evaluable biopsies for all post-dose biopsy time points in the study. A post-dose biopsy will not be required from participants with a non-evaluable pre-dose biopsy; these participants will be candidates for replacement as assessing HSD17B13 knockdown from the post-dose biopsy will not possible with a non-evaluable pre-dose biopsy. To replace biopsies as needed, new participants will be added to the appropriate dose cohort by forced treatment allocation. The rationale for forced treatment allocation includes the small sample size per dose cohort, limiting exposure due to the invasive nature of biopsy, and the lack of existing safety exposure on doses above 200 mg. The recruitment of additional participants may take place when the study team identifies that a dose cohort is at risk of not reaching the minimum required number of 5 evaluable participants. The full participant addition implementation procedure will be detailed in the RCCS.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, [3] telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the laboratory manual.
- Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. Participants who have signed informed consent but are not eligible to proceed should be recorded in the eCRF with a status of 'screen failure'.
- Procedures conducted as part of the participant's routine clinical management (e.g., for diagnosis by historical liver biopsy [histology]) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- In the event of a significant study-continuity issue (e.g., caused by a pandemic), alternate strategies for participant visits, assessments, study intervention distribution and monitoring may be implemented by the Sponsor or the investigator, as per local health authority/ethics requirements.

CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Administrative and Baseline Procedures

8.1.1. Collection of Demographic Data

Record demographic data such as year of birth, sex, race, and ethnicity in the participant's eCRF.

Collection of age, sex, race and ethnicity data is necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population.

8.1.2. Medical History

Obtain the participant's medical history by interviewing the participant and/or review of the participant's medical records. Record any pre-existing conditions, signs and/or symptoms present prior to study intervention in the eCRF.

8.2. Target Engagement and Pharmacodynamic Assessments in Liver

Primary and secondary endpoints are presented in Section 3. Planned timepoints for all assessments are provided in the SoA (Section 1.3).

The secondary PD objective and endpoints based on HSD17B13 protein and mRNA expression levels from baseline to post-dose biopsy capture PD by assessing extent of knockdown of HSD17B13 by GSK4532990 as described below.

8.2.1. Liver-Biopsy-Based Assessments

Samples from biopsies collected from the liver at baseline and following a single dose of GSK4532990 (see Figure 4) will undergo analysis to determine hepatic HSD17B13 protein and mRNA expression levels to determine target engagement.

Further specific liver biopsy instructions and details will be further outlined in the Liver Biopsy manual.

8.2.1.1. *HSD17B13* Protein Expression

The effect of GSK4532990 on hepatic HSD17B13 protein expression levels will be assessed using the electrochemiluminescence immunoassay.

8.2.1.2. *HSD17B13* mRNA Expression

The effect of GSK4532990 on hepatic *HSD17B13* mRNA expression will be assessed using reverse transcription-quantitative polymerase chain reaction.

8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.3.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal (including liver and spleen), dermatologic, and neurological systems. Height and weight (on an empty bladder and wearing light clothing) will also be measured and recorded.
- A symptom-directed physical examination will be performed only if the participant indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the investigator or delegate. Significant weight gain or loss may require further physical examination at the discretion of the investigator.
- If an exam is done by a HHS professional, a symptom-directed examination will be performed as outlined in the SoA (Section 1.3).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2. Vital Signs

- Temperature, pulse rate, respiratory rate, and blood pressure should be assessed prior to blood collection for laboratory tests.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
    - Blood pressure and pulse measurements should be taken sitting and preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
    - One pulse and 3 blood pressure measurements will be taken. For blood pressure measurements, 3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute. The average of the 3 blood pressure readings will be recorded.

8.3.3. Electrocardiograms

- Triplicate 12-lead ECGs will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.
- The QTc is the QT interval corrected for heart rate according Fridericia's formula (QTcF). It is either machine-read or manually over-read.
    - Fridericia's formula:

$$\text{QTcF (ms)} = \frac{QT\ (ms)}{\sqrt[3]{RR\ (ms)/1000}}$$

- ECG readings should be taken after 5 minutes rest in the supine position.

- At each timepoint at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart.

8.3.4. Clinical Safety Laboratory Tests

- See Section 10.2 for the list of clinical laboratory tests to be performed in accordance with laboratory manual and the SoA (Section 1.3).
- If allowed by country regulation/ethics, clinical safety laboratory sampling may be conducted remotely by an HHS professional.
- If allowed by country regulation/ethics, clinical safety laboratory sampling ancillaries can be shipped DTP from the [investigational site/depot] to the [participant's home address/other location]. Collected laboratory samples can also be collected DFP from the [participant's home address/other location] to the [central laboratory/investigational site]. The process for this shipment must be agreed with GSK who will provide operational details.
- The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition, unless these abnormal laboratory findings fulfill the criteria for liver monitoring and should be reported as an SAE (see Section 10.7)
- All laboratory tests with values considered clinically significantly abnormal during participation in the study to the EoS study visit (per the SoA [Section 1.3]) or a minimum of 120 days after study intervention administration (whichever is later) should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - In the absence of a diagnosis, abnormal laboratory findings assessments or other abnormal results the investigator considers clinically significant will be recorded as an AE or SAE, if they meet the definition of an AE or SAE (refer to Section 10.3.1 and Section 10.3.2).
    - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the Sponsor notified.
    - If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE), then the results must be recorded.

8.3.5. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative.
- Pregnancy testing (serum) should be conducted at screening prior to study intervention administration.
- Female participants of childbearing potential must perform a urine pregnancy test before the administration of study intervention.
- Pregnancy testing (urine) should be conducted at the end of relevant systemic exposure (to EoS visit per the SoA [Section 1.3].
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.
- Refer to Section 8.4.6 for the information on study continuation for participants who become pregnant during the study.

8.3.6. Study Holding Rules, Safety Monitoring, and Committees

- Participant safety will be continuously monitored by the Medical Monitor, designated Safety Lead (or delegate) and Sponsor's internal committees, throughout the study. Pertinent findings and conclusions are shared with the product's SRT for review of the overall benefit-risk profile of the product.
- A DEC will review data defined in the DEP for making dose escalation decisions (see Section 4.4). The DEP will describe the composition of the DEC, criteria for review and quality control of data required for a dose escalation decision, and appropriate documentation of the dose escalation or selection decisions. The DEP plan will describe the required data review and documentation of the dose escalation or selection decisions. The decision to proceed to the next dose level of GSK4532990 or modify doses is made by the Sponsor's internal DEC.
- The dosing schedule may also be adjusted to expand or reduce a dosing cohort to further evaluate [safety, PK and/or PD] findings at a given dose level or to add cohorts to evaluate up to 1 additional dose level. The study procedures for these additional participant(s)/cohort(s) will be the same as those described for other study participants/cohorts.
- The above criteria will apply even if measured PK parameters are below the prespecified PK stopping criteria, and every effort will be made to take a blood sample at the time of the AE for PK analysis.
- In addition, an iDRC will conduct an aggregate review of safety, PK and PD data where available at predefined timepoints during the study to assess safety and target engagement and inform internal decision-making (see Section 9.4).

- Should continuous monitoring of participant safety identify pertinent findings that do not meet the pre-specified dose escalation stopping criteria but are considered to have the potential to impact participant's safety, the Sponsor will, following internal governance processes, review the relevant data. During that review, the Sponsor will consider
  a. whether there is a need to temporarily pause dosing of GSK4532990 either at all doses or at specific doses, and/or
  b. whether enrollment should be temporarily paused during the review.
- If an initial decision is made to pause dosing or study enrollment, following completion of the review and based on the totality of available safety data, a decision will be made by the Sponsor's internal governance as to whether further dosing of participants and enrollment in the study will be allowed to resume (with or without modifications).

8.4. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

For definitions relating to safety information see Section 10.3.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and other safety information and remain responsible for following up all AEs (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.4.1. Time Period and Frequency for Collecting AE, SAE, and Other Safety Information

All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA.

All AEs will be collected from the start of study intervention until the follow-up visit at the timepoints specified in the SoA.

Medical occurrences that are not SAE, which begin before the start of study intervention but after obtaining informed consent and are not resolved before study intervention is administered will be recorded as medical history/current medical conditions, not as AEs.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3 and Section 8.4.5. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

A poststudy AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, after a participant has been discharged from the study, the investigator must record it in the medical records. If the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

8.4.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 8.4.4) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.4.4. AESIs

8.4.4.1. Injection Site Reactions

ISRs are any experiences which occur at the site of injection of the study treatment. Injection site reactions were the most commonly reported treatment-related adverse event in the Phase 1/2a study with GSK4532990. Injection site reactions included, but were not limited to, erythema, swelling and bruising.

Injection site reactions will be assessed throughout durations of the in-house stay for participants and any ISRs that arise during this time will be followed-up by the PI or delegated clinical staff until the resolution.

ISRs will be graded based on the latest version (Version 5.0) of the CTCAE criteria:

- Grade 1: Tenderness with or without associated symptoms (e.g., warmth, erythema, itching).
- Grade 2: Pain; lipodystrophy; edema; phlebitis.
- Grade 3: Ulceration or necrosis; severe tissue damage; operative injection indicated.
- Grade 4: Life threatening consequences; urgent injection indicated.
- Grade 5: Results in death.

The PI and delegated clinical staff are responsible for detecting, recording, and reporting ISRs. The location and extent of any ISR should be clearly reported. Should a participant experience an ISR at more than one injection site (where applicable), each ISR should be reported as a separate AE. ISRs will be considered as an AESI. The PI and delegated clinical staff may consider referral to a dermatology specialist where clinically indicated.

8.4.4.2. Hepatic Events

Hepatic events have been reported with other siRNAs. Whilst the potential for off-target effects is not anticipated with GSK4532990, a strategy for liver-related monitoring has been developed (see Section 10.7.1). All liver laboratory findings requiring increased monitoring will be considered an AESI.

8.4.5. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met. See Section 8.4.1 for reporting timeframes.
- For SAEs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in Section 10.3.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Table 12 Timeframes for Submitting SAE, Pregnancy and Other Events Reports to GSK

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours[a, c]	Adverse Events Report	24 hours[a]	Adverse Events Report
Pregnancies	24 hours[a]	Pregnancy Notification/ Report	24 hours[a]	Pregnancy (follow-up) Report
AESIs	24 hours[b, c]	Adverse Events Report	24 hours[a]	Adverse Events Report

a. Timeframe allowed after receipt or awareness of the information by the investigator/site staff.
b. Timeframe allowed once the investigator determines that the event meets the protocol definition of an AESI.
c. Paper Adverse Events Report will be dated and signed by the investigator (or designee). For each SAE/AESI, the investigator(s) must document in the medical notes that they have reviewed the SAE/AESI and have provided an assessment of causality.

8.4.6. Pregnancy

Female participants who become pregnant after administration of the study intervention will be withdrawn from the study.

- Details of all pregnancies in female participants will be collected after the start of study intervention until the EoS visit (per the SoA [Section 1.3]).

- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female participant pregnancy.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. See Table 12 (Section 8.4.5) for reporting timeframes.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor as described in Table 13. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

8.4.7. CV and Death Events

For any CV events detailed in Section 10.3.3 and all deaths, whether or not they are considered SAEs, specific CV, and Death sections of the CRF will be required to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-CV death.

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific CV section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death eCRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

8.4.8. Contact Information for Reporting SAEs, AESIs, and Pregnancies

Table 13 Contact Information for Reporting SAEs, AESIs, and Pregnancies

Study contact for questions regarding SAEs, AESIs, and pregnancies Contact GSK's local and/or medical contacts
Contacts for reporting SAEs, AESIs, and pregnancies Available 24/24 hours and 7/7 days Email: uk.gsk-rd-gcsp-ctsm-admin@gsk.com Fax: +44(0) 20 81814780

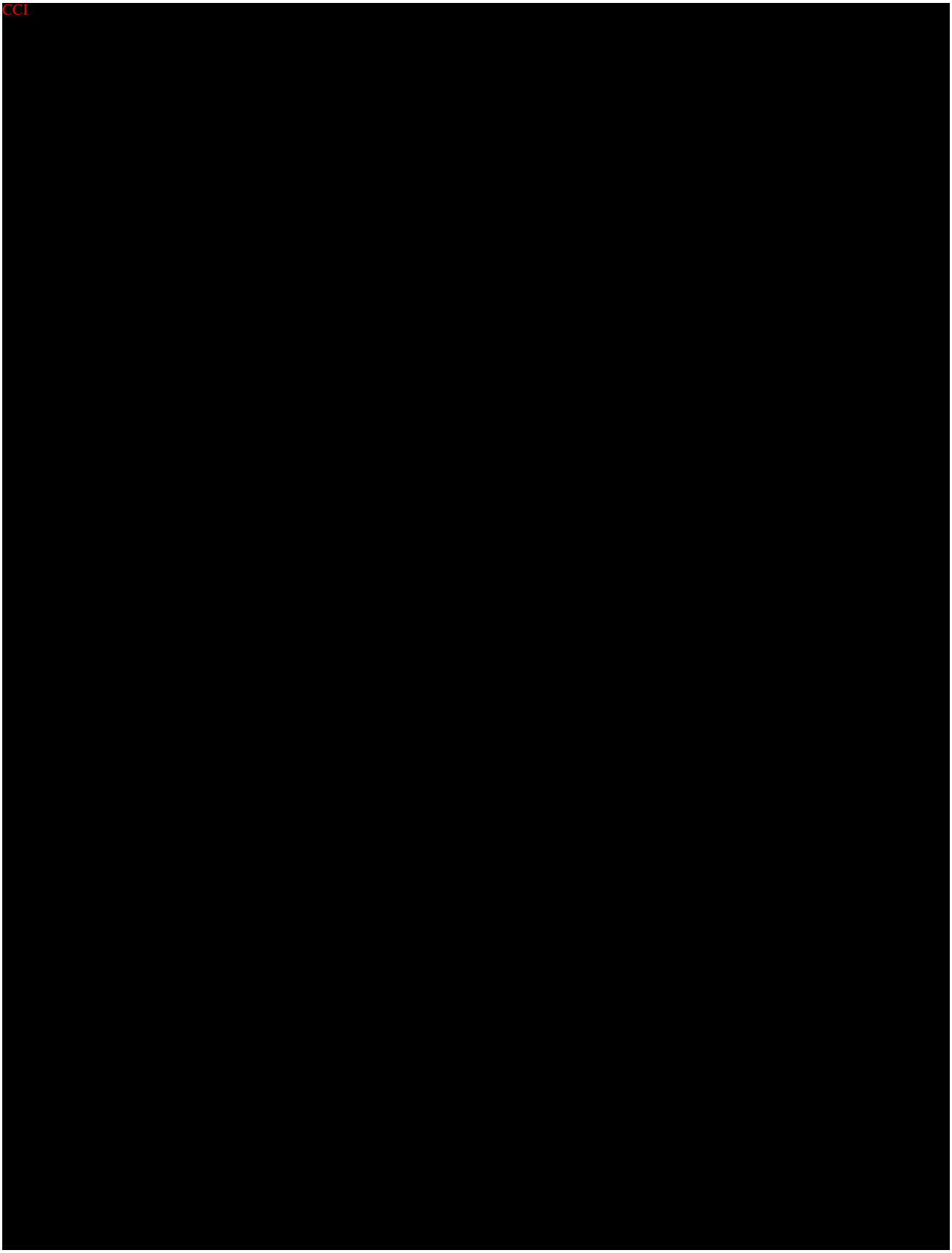
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[redacted]

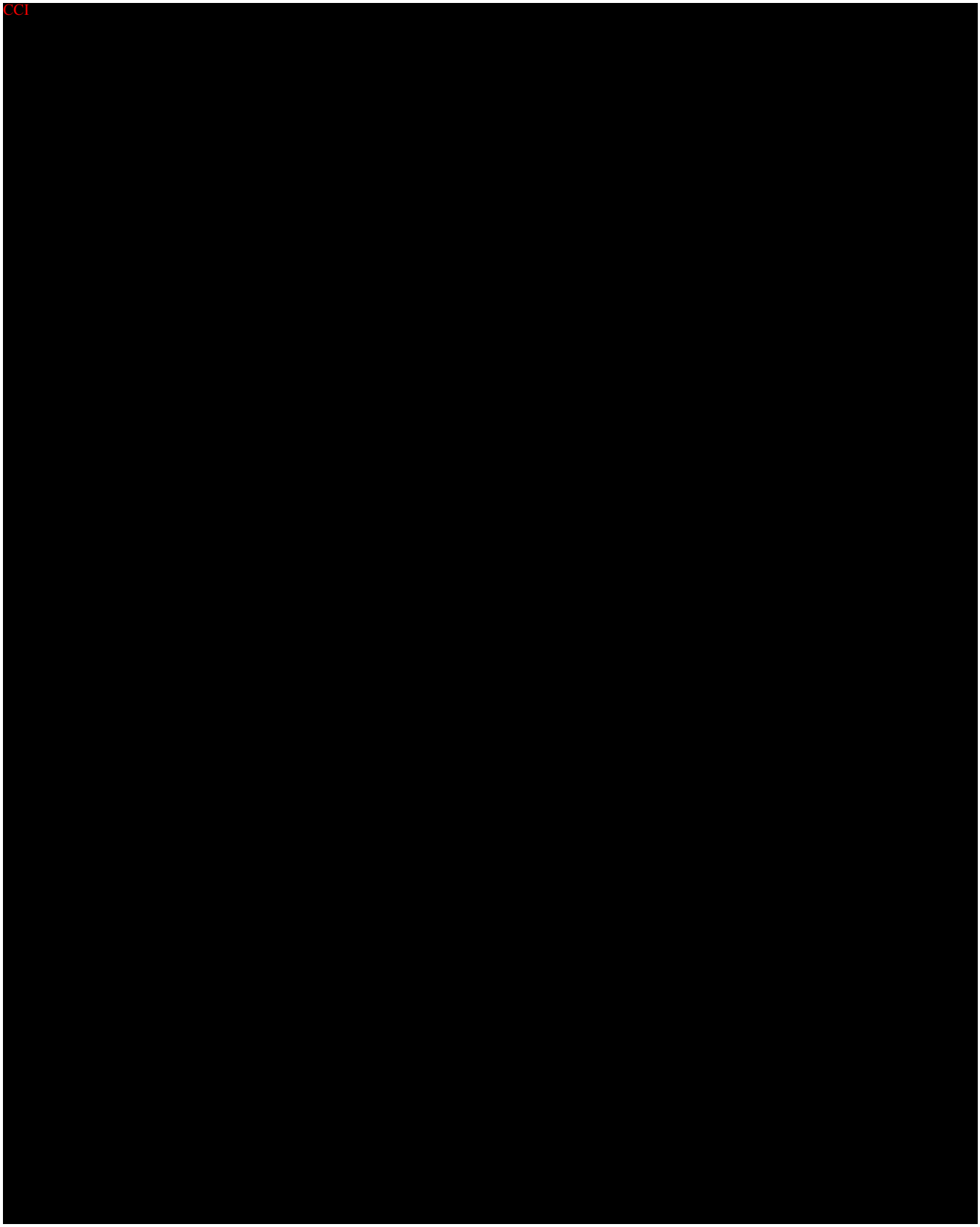
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[redacted]

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[redacted]

8.8. Immunogenicity Assessments

Not applicable for this study.

9. STATISTICAL CONSIDERATIONS

The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1. Statistical Hypotheses

9.1.1. Primary Endpoints

As outlined in Section 3, the primary objective of the statistical analysis of the study is to predict the mean and 95% CI of percent change from baseline of HSD17B13 protein and mRNA expression levels, derived from the PK-PD target engagement model at each treatment arm and post-dose biopsy time. Estimating the mean change from the target engagement model does not feature hypothesis testing.

9.1.2. Multiplicity Adjustment

Given there are no planned hypothesis tests, there are no plans for multiplicity adjustment.

9.2. Analysis Sets

For the purposes of analyses, the following populations are defined in Table 14.

Table 14 Analysis Sets

Analysis Set	Definition/Criteria	Analyses Evaluated
Screened	All participants who were screened for eligibility.	Study Population
Enrolled	All participants who entered the study (who were allocated to a dose cohort or received study intervention or underwent a post screening study procedure). Note: screening failures (participants who never passed screening even if rescreened) and participants screened but never enrolled into the study (met eligibility but not needed) are excluded from the Enrolled analysis set as they did not enter the study.	Study Population
Safety/Exposed/Biomarkers	All participants who received single dose of study intervention.	Safety/Biomarkers
HSD17B13 Protein Concentration Analysis Set	All participants in the Enrolled analysis set and have evaluable baseline and/or post-dose biopsy protein assessments.	PK/PD target engagement
HSD17B13 mRNA Concentration Analysis Set	All participants in the Enrolled analysis set and have evaluable baseline and/or post-dose biopsy mRNA assessments.	PK/PD target engagement
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9.3. Statistical Analyses

9.3.1. General Considerations/Definitions

Final analyses will be performed after the completion of the study and final dataset authorization. Where appropriate, baseline assessment is the last available assessment prior to the time of dosing.

9.3.2. Primary Endpoints/Estimands Analysis

Details of estimand strategies for primary endpoints can be found in Section 3. The primary analysis will fit the target engagement model of GSK4532990 inhibition of HSD17B13 protein and mRNA expression. The following analyses will be performed for the primary endpoints:

Endpoints	Statistical Analysis method
Pre and post dose liver biopsy-derived HSD17B13 protein expression levels	The primary objective of this analysis is to estimate mean and 95% prediction interval of percent change from baseline of HSD17B13 protein and mRNA derived from the PK-PD target engagement model at each treatment arm and post-dose biopsy time. The HSD17B13 protein and mRNA concentrations obtained from pre-dose and post-dose biopsy samples will be used in the analysis. Nonlinear mixed effect modelling utilizing standard PK-PD approach in accordance with applicable EMEA (2008) and FDA (2022) guidance documents will be applied as the data permit. The PK-PD target engagement model can principally be partitioned into a structural model, a stochastic model, and a covariate model.

Endpoints	Statistical Analysis method
	The structural model will describe *HSD17B13* mRNA/protein in a typical NASH patient and how GSK4532990 affects *HSD17B13* mRNA/protein over time after a single SC administration. Covariates will be considered based on underlying scientific rationale and their potential significant impact on the population PK-PD parameters. A target engagement model, once fitted, will be used to estimate the mean and 95% prediction interval of percent change from baseline of HSD17B13 protein and mRNA at each treatment arm and post-dose biopsy time. If problems are encountered fitting the base target engagement model to the data, then additional models will be investigated until an appropriate model can be chosen. Further details on the modelling approach will be included in the SAP. Strategies for handling ICEs are described in Section 3 . For participants with intercurrent events of prohibited medication, increase in self-reported alcohol consumption, or delays in timing of post-dose biopsy, all observations following any of these intercurrent events will be included in the analysis set for the primary estimand. All participants in the HSD17B13 protein and mRNA concentration analysis set will be included in the target engagement model. Post-dose missing data for any reason will be ignored in the nonlinear mixed effects model for the primary endpoint and will not be imputed. For the additional estimand of the primary objective, observations following use of prohibited medication or increase in self-reported alcohol consumption will be ignored whereas observations following delays in timing of post-dose biopsy will be included.
Pre and post dose liver biopsy-derived *HSD17B13* mRNA expression levels	The *HSD17B13* mRNA concentration analysis set will be used. The same methods will be used as above for the first primary estimand.

9.3.3. Secondary Endpoints/Estimands Analyses

The following analyses will be performed for the secondary endpoints:

Endpoints	Statistical Analysis Method
• Percent change from baseline in HSD17B13 protein expression levels at each assigned post-dose biopsy time: Weeks 8, 12 or 28 post-dose • Percent change from baseline in *HSD17B13* mRNA expression levels at each assigned post-dose biopsy time: Weeks 8, 12 or 28 post-dose	Percentage change from baseline for protein expression levels will use the HSD17B13 Protein Concentration Analysis Set. Percentage change from baseline for mRNA expression levels will use the *HSD17B13* mRNA Concentration Analysis Set. All data, including any missing data, will be summarized for each treatment arm and biopsy time where applicable. Descriptive statistics will be provided, which may include n, mean and 95% confidence intervals (CI), standard deviation (SD), median, min/max and geometric mean with 95% CI. For participants with non-missing baseline and post-dose biopsies, percent change data will be summarized by assigned biopsy time. For participants whose post-biopsy time falls outside the visit window, additional summaries will include both assigned and actual post-biopsy times. Additional exploratory analyses (e.g., dose-response analysis) may be carried out with details provided in the SAP.

Endpoints	Statistical Analysis Method
Exposure parameters • Area under the concentration-time curve from time zero (pre-dose) to the last quantifiable concentration (AUC0-t) • Maximum observed concentration (Cmax)	The PK analysis set will be used. All data, including any missing data, will be summarized for each treatment arm where applicable. Descriptive statistics will be provided, which may include n, mean and 95% confidence intervals (CI), standard deviation (SD) on both untransformed and log-transformed scale where appropriate, median, min/max, geometric mean with 95% CI.

Further details of the planned analysis of secondary estimands will be described in the SAP.

9.3.4. Safety Analysis

Endpoints	Statistical Analysis Method
Safety • Occurrence of AEs and SAEs • Change from baseline in vital signs at each visit assessment • Change from baseline in key laboratory measurements at each visit assessment • Occurrence of clinically significant ECG findings at each visit assessment	The safety/exposed analysis set will be used. No formal statistical modelling will be applied to any safety endpoint. Population summary statistics will be provided for all safety data by dose. AE and SAE summaries will include frequencies and percentages. Changes from baseline for key laboratory values and vital signs will be summarized by treatment dose. In addition, the number and percentage of participants with values outside the potential clinical importance range will also be summarized. Clinically significant ECG findings will be summarized by number and percentage of participants by treatment arm. The number of events experienced per participant will also be summarized.

9.3.5. Exploratory Endpoint(S)/Estimand(S) Analysis

The description of the planned analysis of exploratory endpoints will be described in the SAP.

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9.5. Sample Size Determination

The adjusted target sample size is 48 participants who will be included in the analysis of the primary estimand and provide sufficient precision to the study and account for missing biopsy data. This study design results in 12 participants in each treatment arm, and within each treatment arm, 6 participants will be assigned to one of two biopsy time points.

The sample size estimation was based on the minimum number of subjects and pre- and post-dose HSD17B13 protein and mRNA samples required to estimate the PK/PD target engagement model parameters with good precision and bias. The target engagement model is developed to describe the baseline and post-dose changes in hepatic HSD17B13 protein and mRNA concentrations as a result of GSK4532990 at multiple timepoints and at different dose levels. The ability of the target engagement model to calculate the change in HSD17B13 protein and mRNA is dependent upon the estimation of the fixed and random effect parameters with good precision, acceptable parameter bias and normalized root mean square error.

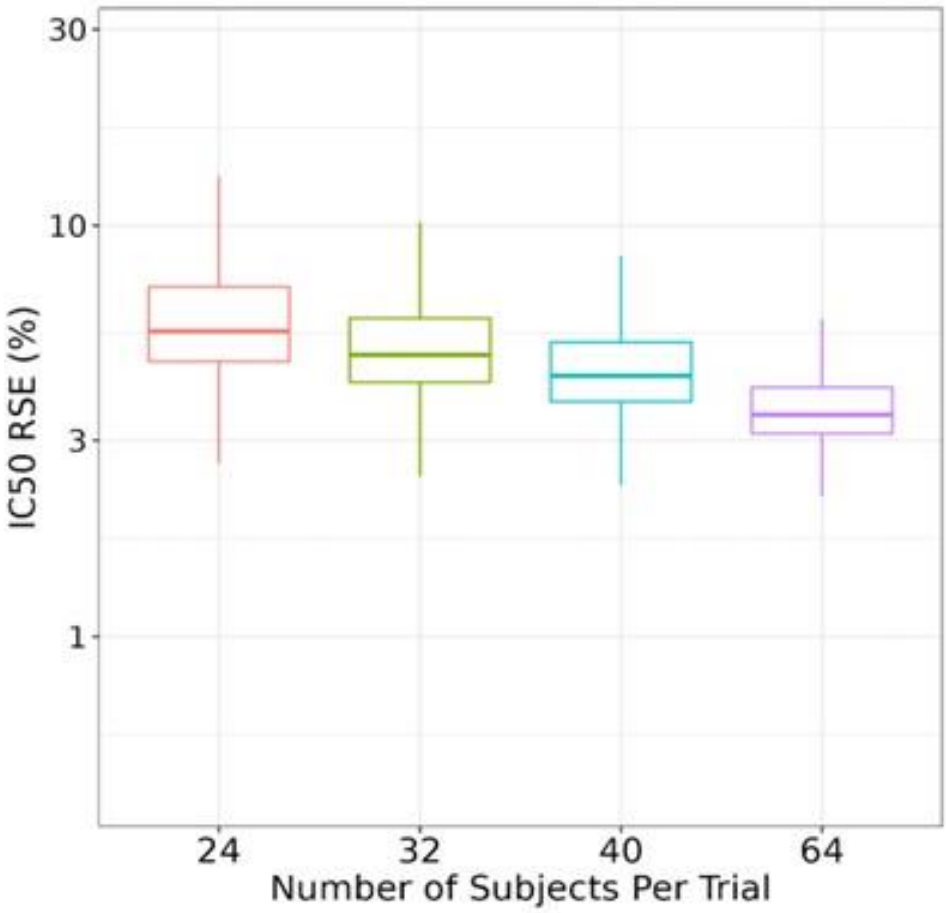
A target engagement model has been developed utilizing data from AROHSD1001 with assumptions for maximum drug effect and *HSD17B13* degradation rates. Thus, the purpose of this study is to examine the validity of those assumptions by accurately estimating all parameters in the target engagement model which will lead to precise estimation of baseline and post GSK4532990 knockdown of HSD17B13 protein and mRNA levels. Therefore, this exercise involved optimal design evaluation using virtual trial simulations and target engagement model re-estimation. The simulations focused on the impact of sample size on the estimation of IC50, one of the fixed effect parameters of

primary interest. Based on these simulations, the SAP will also provide summaries of the expected precision for the predicted percent change of the HSD17B13 protein and mRNA levels from baseline for the different treatment arms and biopsy times of the study.

The model was used to generate a "global" dataset with baseline and daily changes in hepatic HSD17B13 protein due to GSK4532990 by simulating individual participant level PK and PD parameters ("true parameter estimates") for each participant over a single dose range of 25 mg to 800 mg. This dataset was used for random sampling without replacement to create virtual clinical trial designs varying the number of participants per treatment arm, the number of participants per timepoint, and the biopsy sample time points. Each clinical trial was used to estimate PK parameters in the target engagement model for each set of N patient/timepoint for 1000 trials. Results from the target engagement model estimation were compared to the "true parameter estimates" based on final fixed and random effect parameter estimates of the target engagement model estimated with good precision (% relative standard error) <10% for each simulated trial design.

The results of the target engagement model estimation parameter precision are provided in Figure 4.

Figure 4 IC50 Relative Standard Error (%) Across 1000 Trials of Varying Sample Size. Simulations Assume Equal Number of Participants Across Each of the 4 Doses and 2 Biopsy Time Points



All tested sample sizes performed adequately and increasing the sample size resulted in decreasing relative standard errors (RSE). A sample size of 40 participants equally allocated across 4 doses and 2 biopsy times with evaluable baseline and post-dose biopsy assessments was chosen for this study. The sample size N=40 provided sufficient confidence in the estimation of target engagement model parameters and inter-subject variability for further modelling and simulation to support dose selection in future clinical development. These 40 evaluable participants with a 30-fold dose range (25 to 800 mg) will allow adequate estimation of the full dose—exposure-response curve based on extent and duration of GSK4532990 target engagement (hepatic HSD17B13 protein and mRNA knockdown). This total sample size was adjusted for an anticipated 15% of non-evaluable biopsy assessments, giving a total of N=48 for the entire study, with 6 individuals assigned to each of 4 doses and 2 biopsy time points. In summary, these simulations also indicated that 5 participants with evaluable biopsy assessments at baseline and post-dose biopsy time points for each dose cohort would be sufficient to estimate the protein knockdown with adequate precision for the proposed target engagement model.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS international ethical guidelines
  - Applicable ICH GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC

- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participants and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They will be required to physically or digitally sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that physical or digital informed consent was obtained before the participant was enrolled in the study and the date the physical or digital consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A physical or digital copy of the ICF(s) must be provided to the participant.
- Participants who are rescreened are required to sign a new ICF.
- The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.
- In case of unexpected pregnancy, participant must be informed that personal information such as date of birth, and sex of the baby will be collected as part of safety follow-up. Consent for the baby may be obtained from the participant and/or their partner as per local regulations.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.
- The participant must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant, that their data to be used as described in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between Sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. GSK and/or trusted third parties working on behalf of GSK and/or institutions working with GSK for the purposes of this study are contractually bound to protect participant coded data. GSK will protect participant coded data and will only share it as described in the ICF.
- GSK has a global, internal policy that requires all GSK staff and complementary workers to report data incidents or breaches immediately, using dedicated tools. Clear procedures are defined for assessing and investigating data breaches to identify and to take appropriate remediation steps, to contain and to mitigate any risks for individuals resulting from a breach, in compliance with applicable laws.

10.1.5. Committees Structure

Participant safety will be monitored by the Sponsor's internal SRT, iDRC, and by the DEC (see Section 10.1.5.3).

10.1.5.1. Safety Review Team

An SRT is in place for each GSK product. It comprises of a global cross-functional team responsible for the ongoing assessment of benefit-risk for a product. The SRT contributes to the continual assessment of incoming new efficacy and safety information.

10.1.5.2. Internal Data Review Committee

The iDRC will review safety, PD, and PK data at pre-defined time points, the goal of which is to help internal development planning. An initial interim analysis review for this study is planned after Schedules 1 and 2 are enrolled and completed. Additional reviews are planned after Schedule 3 and again after Schedule 6 are enrolled and completed. Please refer to Figure 3 and Table 15 which outlines all of the interim analysis data review time points.

10.1.5.3. Dose Escalation Committee

The DEC will evaluate data for doses >400 mg, given prior experience in the Phase 1/2a and Phase 2b studies at doses up to 200 mg (see Section 4).

The DEC will be used to ensure data integrity in dose escalation decisions by performing clinical data review and appropriate quality control of data prior to making dose escalation decisions for this study. The Committee will review emerging data and safety parameters during the study. The remit, participants, and conduct of the DEC will be outlined in the DEP.

The DEC and is comprised of investigators from investigational site(s) and GSK study team members (including at a minimum the GSK Medical Director/Monitor and cross-function representatives including Clinical Science Lead, Clinical Pharmacokinetist, Study Delivery Lead, Clinical Safety Lead and Biostatistician).

10.1.6. Dissemination of Clinical Study Data

- The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/ study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results, including a summary of trial results understandable to laypersons. The investigator is encouraged to share the plain language summary with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.
- GSK will provide the investigator with the randomization codes and participant-level line listings for their site only after completion of the full statistical analysis.

- GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding. Data will be shared with researchers in a non-identifying way, and appropriate measures will be taken to protect PI; these measures will comply with data protection and privacy laws that apply.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of eCRFs will be provided in eCRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- QTLs will be predefined in the QTL plan to identify systematic issues that can impact participant right, safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring, involvement of central reading mechanism) methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final CSR/equivalent summary unless local regulations or institutional policies require a different retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.
- When copies of source documents are shared externally for review by a central reader mechanism (e.g., endpoint adjudication committee; expert reader), documents are stored by the external body for 25 years.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in Source Data Acknowledgment.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Copies of documents are shared with external third parties contracted by GSK for review by a central reader mechanism (e.g., endpoint adjudication committee; expert reader). The non-exhaustive list of documents shared to inform the central reader may include, discharge summaries, imaging reports, ECG reports etc. Participant names or any information which would make the participant identifiable or is not essential for the central reader mechanism will be redacted by the investigator sites prior to transfer. Details of the list of documents and the redaction procedure are provided in the site manual or equivalent. These documents will be used by the third party solely for the purpose indicated within this protocol.

10.1.9. Study and Site Start and Closure

Start of Study and First Act of Recruitment

The start of study and the first act of recruitment are defined as FSFV at a country-level.

Study/Site Termination

GSK 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 GSK. 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 initiate study-site closure at any time, 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 protocol, the requirements of the IRB/IEC or local health authorities, 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.

If the study is prematurely terminated or temporarily suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or temporary 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.

10.1.10. Publication Policy

The results of this study may be published in peer reviewed scientific literature and/or presented at scientific meetings.

The Sponsor will comply with the requirements for publication of study results in accordance with standard editorial and ethical practice and as per the Sponsor's internal policy.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 16 will be performed by the central laboratory unless otherwise specified.
- Local laboratory results are required at specific visits and in case of a renal or liver event on study and will need to be recorded according to the protocol.
    a. Unscheduled:
        - If CK is ≥ ULN, the site will locally assess urinary myoglobin by direct testing (if possible) or by evaluation of standard urine dipstick for heme/blood and urine microscopy for red blood cells (Table 16).
        - In case of suspected pregnancy, site to locally perform urine or serum pregnancy test (Table 16).

- If suspected drug-induced liver injury: local liver chemistry safety monitoring (AST, ALT, ALP, bilirubin [total and conjugated], and INR).
- If central laboratory results cannot be obtained (perhaps because of disruption associated with a pandemic), investigator discretion can be applied. However, some safety related parameters: hematology, coagulation and clinical chemistry will still be expected.
- Local coronavirus disease 2019 testing if clinically indicated.

- Central laboratory results will also be used for enhanced safety monitoring in the event of suspected nephrotoxicity, rhabdomyolysis, and blood clotting disorders.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Table 16 Protocol-Required Safety Laboratory Tests

Laboratory Assessments	Parameters
Clinical Chemistry[a]	Albumin*
	Alanine aminotransferase (ALT)*
	Alkaline phosphatase (ALP)*
	Aspartate aminotransferase (AST)*
	Blood urea nitrogen (BUN)
	Calcium
	Creatinine*
	Creatine kinase (CK)*
	GGT
	Potassium
	Sodium
	Total and conjugated (direct) bilirubin*
	Total protein
Coagulation	Fibrinogen*
	INR
Hematology	Platelet count
	RBC count
	Hemoglobin
	Hematocrit
	RBC indices:
	MCV
	MCH
	% Reticulocytes
	WBC count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Serum Lipid Profile	Total cholesterol
	HDL cholesterol
	LDL cholesterol

Laboratory Assessments	Parameters
	VLDL-C
	Triglycerides
	Non-HDL-C
Routine Urinalysis	Specific gravity, pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by central dipstick
	Microscopic examination (if blood, nitrites, leukocytes or protein on central dipstick is abnormal)
	Urine albumin:creatinine ratio (at Screening 1; if protein detected on local dipstick; and any unscheduled visit if a renal event occurs)
Other Screening Tests	Follicle-stimulating hormone (as needed to confirm whether a woman is of non-childbearing potential only, refer to Section 10.4)
	Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines)
	Serology (HIV antibody, HBsAg, and HCV antibody).
	Serum pregnancy test (for women of childbearing potential)
WOCBP	Urine pregnancy test by local laboratory (Refer to Section 8.3.5)
Other conditional unscheduled tests	Urinary myoglobin will be assessed locally if CK is ≥ULN
	For a liver event, please refer to Section 10.7.2 (Table 19) for the full list of assessments required.
	For a renal event, please refer to Section 10.7.3 for further information.

* Denotes key laboratory parameters.
a. Liver chemistry samples may be obtained locally for enhanced monitoring in the event of suspected DILI.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of participant's previous therapeutic regimen).

Events NOT Meeting the AE Definition

Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital, admission for routine examination.).

Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. Pre-existing diseases will be recorded in the medical history section of the eCRF.

Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect in the offspring of a study participant

f. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy)

g. Is a suspected transmission of any infectious agent via an authorized medicinal product]

h. Other situations:

- **Possible Hy's Law case: ALT ≥3x ULN AND total bilirubin ≥2x ULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2xULN, and direct bilirubin ≥2xULN and at least doubled from baseline value) or INR >1.5 must be reported as SAE.**
- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Definition of CV Events

CV Definition:
Investigators will be required to fill out the specific CV event page of the eCRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

10.3.4. Definition of TEAE

TEAE Definition:
• A TEAE is an event that emerges during treatment, having been absent pre-treatment or worsens relative to the pre-treatment state.

10.3.5. Recording, Assessment and Follow-up of AE, SAE, and Pregnancies

10.3.5.1. AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK required form.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

10.3.5.2. Assessment of Intensity

The investigator will make an assessment of intensity (severity) for each AE and SAE reported during the study.

The severity of AEs will be graded according to CTCAE v5.0; NIH, NCI. The CTCAE severity Grades 1 through 5 provide unique clinical descriptions of severity of each AE.

The CTCAE v5.0 is available on the NCI/NIH or using the following website link: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

10.3.5.3. Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.3.5.4. Assessment of Outcomes

The investigator will assess the outcome of all serious and nonserious unsolicited AEs recorded during the study as:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved

- Recovered with sequelae/resolved with sequelae
- Fatal (SAEs only).

10.3.5.5. Follow-up of AEs, SAEs, Pregnancies, or Any Other Events of Interest

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

After the initial AE/SAE/pregnancy or any other event of interest, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, nonserious AESIs (as defined in Section 8.4.4) and non-serious AEs considered related to treatment by the investigator will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

Other nonserious AEs must be followed until resolution or the EOS study visit (see Section 4.6 for definition), whichever comes first, or until the participant is lost to follow-up.

Follow-up during the study

AEs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until resolved, stabilized, otherwise explained, the participant is lost to follow-up or the EOS study visit according to the criteria detailed above.

If a participant dies during their participation in the study or during a recognized follow-up period, GSK will be provided with any available postmortem findings, including histopathology.

Follow-up of pregnancies

Pregnant participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the paper pregnancy follow-up report/electronic pregnancy report and the AE Report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs in this study, if the pregnancy outcome is an SAE, it should always be reported as such.

Furthermore, the investigator must report any SAE occurring as a result of a poststudy pregnancy that is considered by the investigator to be reasonably related to the study intervention, to GSK as described in Section 10.3.5.7.

10.3.5.6. Updating of SAE, AESI and Pregnancy Information After Removal of Write Access to the Participant's eCRF

When additional SAE, AESI or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be sent to the Study contact for reporting SAEs (refer to Section 8.4.3).

10.3.5.7. Reporting of SAEs, AESIs and Pregnancies

SAE Reporting to GSK via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone.
- If the site during the course of the study or poststudy becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK non-IMP they will report these events to GSK or to the concerned competent authority via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.
- Contacts for SAE reporting can be found in Section 8.4.8.

SAE Reporting to GSK via Paper Data Collection Tool

- Email/facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the medical monitor.
- In rare circumstances and in the absence of email/facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in Section 8.4.8.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

10.4.1.1. Woman of Childbearing Potential

Women in the following categories are considered WOCBP (fertile):

1. Adolescents of childbearing potential: Tanner stage ≥2 (post-thelarche) irrespective of the occurrence of menarche or following menarche.
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below)

Note: Menarche is the first onset of menses in a young female. Menarche is normally preceded by several changes associated with puberty including breast development and pubic hair growth.

10.4.1.2. Woman of Nonchildbearing Potential

Women in the following categories are considered WONCBP:

1. Premenarchal: Tanner stage 1 (prepubertal)
2. Permanently sterile due to one of the following procedures:
    a. Documented hysterectomy
    b. Documented bilateral salpingectomy
    c. Documented bilateral oophorectomy
        - For permanently sterile individuals due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry. If reproductive status is questionable, additional evaluation should be considered.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance

Male participants with female partners of childbearing potential are not required to use contraception.

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective contraceptive method consistently and correctly according to the methods listed in GSK's list of highly effective contraceptive methods from the time of the negative serum pregnancy test at screening and for at least 28 days before study intervention; during study intervention; and for up to the EOS study visit (see Section 4.6 for definition) or a minimum of 120 days after study intervention administration, whichever is later.

Table 17 Highly Effective Contraceptive Methods

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
Implantable progestogen-only hormone contraception associated with inhibition of ovulation
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)
Bilateral tubal occlusion/ligation
Azoospermic partner (vasectomized or due to a medical cause) • *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male partner can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
• **Highly Effective Methods[b] That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal • injectable
Progestogen-only hormone contraception associated with inhibition of ovulation • oral • injectable
Sexual abstinence • *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

[b.] Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction).

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10.6. Appendix 6: Study Stopping Criteria

The criteria outlined below for adverse events, suspected liver failure and injection site reactions will, if met, trigger review by the iDRC and/or GSK internal governance to consider the following outcomes:

a. Pause further study recruitment to conduct further investigation/review.

b. Pause further study recruitment and dosing of recruited participants to conduct further investigation/review.

c. Permanently stop further recruitment into the study.

d. Permanently stop further recruitment into the study and permanently stop further dosing for all recruited participants.

e. Continue recruitment and further dosing of recruited participants after protocol modifications.

f. Continue recruitment and dosing of recruited participants with no protocol modifications.

If enrollment or dosing is paused for the study overall the appropriate notifications will be made to regulators as required per local requirements. The study may be resumed (with or without modifications) only after further review of all available safety data and notification and / or agreement by the appropriate regulatory agencies as appropriate.

10.6.1. Adverse Events

- First occurrence of a CTCAE Grade 5 TEAE or laboratory abnormality (confirmed by repeat testing) that is considered to be at least possibly related to GSK4532990.
- Two or more study participants developing the same CTCAE Grade 4 TEAE or laboratory abnormality (confirmed by repeat testing) considered to be at least possibly related to GSK4532990.
- Three or more study participants developing the same CTCAE Grade 3 or higher TEAE or laboratory abnormality (confirmed by repeat testing), all considered to be at least possibly related to GSK4532990.

10.6.2. Suspected GSK4532990-Induced Liver Failure

Two or more study participants suffer from suspected GSK4532990-induced liver failure. For the 2 or more cases of suspected liver failure, all of criteria A-D should be met:

A	Whichever comes first: • ALT[a] ≥x3 ULN, • AST[a] ≥x3 ULN, • ALP ≥x3 ULN, • ALT[b] ≥2x participant's BLN ALT, • AST[b] ≥2x participant's BLN AST, • ALT ≥300 U/L, • AST ≥300 U/L, ***OR*** • ALP ≥300 U/L
B	• TBL ≥2x ULN (≥35% direct bilirubin)

C	• INR ≥1.5
D	• Absence of other credible etiology

a. If participant's baseline average ALT or AST is within normal limits
b. If participant's baseline average ALT or AST is abnormal (>ULN)

10.6.3. Injection Site Reactions

One or more study participants experience a CTCAE Grade 3 ISR.

10.7. Appendix 7: Safety Monitoring Criteria

10.7.1. Liver Safety Monitoring Criteria

10.7.1.1. Reporting of Events Meeting Liver Monitoring Criteria

All liver events requiring increased monitoring should be reported as an AESI (See Section 10.3). In addition, all events of ALT ≥ 3xULN and total bilirubin ≥ 2xULN (when conjugated (direct) bilirubin is ≥ 35%) or ALT ≥ 3xULN and INR ≥ 1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (see Section 8.4 on AESIs).

10.7.1.2. Establishing Baseline Average ALT and AST

In order to establish a robust baseline ALT and AST for subsequent safety monitoring, liver chemistry from the central laboratory should be tested at least twice prior to dosing and an average calculated (the BLN ALT and the BLN AST). The interval between successive ALT and AST tests to calculate the BLN should be ≥14 days. ALT and AST values during the screening window and at Baseline (Day 1) will be included in the BLN calculation for efficacy and routine safety monitoring and increased safety monitoring in the event of suspected DILI.

If the calculated BLN is less than the ULN, the ULN should be used to guide safety monitoring. If the calculated BLN is greater than the ULN, the BLN should be used to guide safety monitoring.

10.7.1.3. Post-baseline ALT and AST Elevations Requiring Increased Monitoring

If any of the criteria specified in Table 18 are met, close monitoring and workup for alternative etiologies (Table 19) should be initiated.

Participants must be monitored at least twice weekly until liver chemistry abnormalities (ALT, AST, alkaline phosphatase, bilirubin, and INR) return to within x1.5 baseline values and ALT ≤ 3xULN. Upon completion of the safety follow-up procedures (Table 19), the participant should attend visits specified in the SoA.

Table 18 ALT and AST Monitoring Criteria

ALT or AST	Bilirubin or INR	Symptoms or Signs[c]	Action
≥5x ULN[a] ≥3x BLN OR ≥300 U/L (whichever comes first)[b]	Normal	None	• Repeat ALT, AST, ALP, INR and bilirubin in 48h[f]. • Assess for development of symptoms • Evaluate for competing etiologies. • Notify the GSK medical monitor within 24 hours of becoming aware of the event[d,f]
≥3x ULN[a] ≥2x BLN[b]	Normal	Present	
≥8x ULN[a] ≥5x BLN OR ≥500 U/L (whichever comes first)[b]	Normal	None	• Place participant in close observation and monitoring as per FDA guidance[e]. • Monitor symptoms. • Evaluate for competing etiologies. • Notify the GSK medical monitor within 24 hours[f]
≥5x ULN[a] ≥3x BLN OR ≥300 U/L (whichever comes first)[b]	Normal, or TBL ≥2xULN, or DBL ≥2x ULN (or ≥0.5 mg/dL) if participant has Gilbert's syndrome or INR ≥1.5 (confirmed)	Present	
≥3x ULN[a] ≥2x BLN OR ≥300 U/L (whichever comes first)[b]	TBL ≥2x ULN, or DBL ≥2x ULN (or ≥0.5 mg/dL) if participant has Gilbert's syndrome, or INR ≥1.5 (confirmed)	None or present	

a. Use this rule if BLN ALT/AST calculated in screening is <ULN for ALT/AST
b. Use this rule if BLN ALT/AST calculated in screening is ≥ULN for ALT/AST
c. New or worsening fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
d. Repeat testing should be performed within 48 hours
e. FDA guidance 2009: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, for additional information
f. Notification to the MM should be made within 24 hours and repeat testing should be performed within 48 hours of the site becoming aware of the event.

These criteria are adapted from consensus guidelines for detection, assessment and management of suspected drug-induced liver injury during clinical trials in patients with NASH [Regev, 2019].

10.7.1.4. Post-baseline ALP Elevations Requiring Increased Monitoring

Close monitoring and workup for alternative etiologies should be initiated if:

- ALP ≥2x ULN with concomitant elevation of total bilirubin (TB) >2x ULN (or direct bilirubin (DB) >0.6 mg/dL if participant has Gilbert's syndrome); or.
- ALP >2x ULN in presence of INR >1.5x ULN or presence of symptoms.

If either of these conditions are met, participants should be closely monitored according to schedule of assessment and until the outcome is resolved i.e., abnormality normalizes, stabilizes, or reaches back to baseline values; or an alternative clinical outcome has occurred (morbidity or mortality).

10.7.2. Follow-up Assessments to be Conducted if Increased Liver Monitoring Criteria are Met

Should any of the post-baseline liver laboratory assessments meet the criteria in Section 10.7.1.3 and/or Section 10.7.1.4, follow-up assessments specified in Table 19 should be carried out to establish possible etiology.

Table 19 Required Follow-up Assessments When Criteria for Increased Monitoring are Met

Required Follow up Assessments

• Central viral hepatitis serology[a]
• Obtain INR and recheck with each liver chemistry assessment until the aminotransferase's values show downward trend.
• Obtain central lab blood sample for PK analysis if event occurs within 2 days after dose. Record the date/time of the PK blood sample collection and the date/time of the last dose of study treatment prior to blood sample collection on the CRF. If the date or time of the dose is unclear, provide the participant's best approximation.[b] Instructions for sample handling and shipping are included in the lab manual.
• Obtain serum CK, LDH, GGT, and serum albumin.
• Fractionate bilirubin if total bilirubin ≥2xULN.
• Fractionate ALP isoenzymes if ALP ≥2xULN.
• Obtain complete blood count with differential to assess eosinophilia.
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the liver event form.
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs, and other over the counter medications.
• Record alcohol use on the liver event alcohol intake form and obtain blood biomarker for alcohol consumption (central lab blood phosphatidylethanol).
• Central lab alpha-1 antitrypsin, anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, anti-mitochondrial antibody, perinuclear anti-neutrophil cytoplasmic antibodies, anti-soluble liver antigen, and quantitative total IgG or gamma globulins.
• Central lab ferritin, transferrin saturation, ceruloplasmin, and copper.
• Serum acetaminophen adduct assay should be conducted (where available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use very unlikely in the preceding week (e.g., where the participant has been resident in the clinical unit throughout).
• Liver imaging (ultrasound, magnetic resonance, or computed tomography) to evaluate liver disease: complete Liver Imaging form.
• Liver biopsy may be considered and discussed with local specialist if available:
  ○ In participants when serology raises the possibility of autoimmune hepatitis
  ○ In participants when suspected DILI progresses or fails to resolve

Required Follow up Assessments
○ In participants with acute or chronic atypical presentation. • If liver biopsy conducted: complete liver biopsy form.

a. Includes: hepatitis A serology, IgM antibody; HBsAg and HBcAb; hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); hepatitis E IgM antibody, and glutamate dehydrogenase.

b. If the date/time of the last dose cannot be approximated or a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample.

10.7.3. Renal Monitoring

Serum creatinine will be measured as per SoA. For an increase from baseline in serum creatinine ≥0.3 mg/dL (26.5 µmol/L), participants will be asked to return to the clinic within 72-96 h of the original test for repeat testing and in addition, a urine sample will be collected for urinalysis and microscopy. A further urine sample will also be collected and stored as per SoA and may be analyzed at the end of the study to better characterize the potential renal injury.

If on repeat testing, either of the 2 following scenarios occurs, the participant will be monitored until the serum creatinine level resolves, stabilizes, or returns to within 1.3x baseline value.

- The increase from baseline for the repeated creatinine value is ≥0.5 mg/dL (44.2 µmol/L), irrespective of whether there are any urinalysis and/or urine microscopy changes; or
- The increase from baseline for the repeated creatinine value is ≥0.3 mg/dL (26.5 µmol/L) **and** the participant has accompanying UACR ≥500 mg/g **or** ≥2x the baseline UACR

For all increases from baseline, upon re-test, in serum creatinine ≥0.3 mg/dL (26.5 µmol/L), the PI and delegated clinical staff will evaluate intercurrent events, laboratory tests and concomitant medications to ascertain cause of renal event.

If on repeat testing:

- The increase from baseline for repeated creatinine value is <0.3 mg/dL (26.5 µmol/L) **and** the participant has UACR <500 mg/g **and** less than twice the baseline UACR, then the participant will be monitored according to the standard SoA timing.

10.7.4. Monitoring Criteria for Elevations in CK

Serum CK will be measured as per SoA. In the event of elevations in serum CK ≥ ULN, urinary myoglobin will be assessed. If CK is elevated, the participant should be evaluated for symptoms of muscle injury including myalgia and discussed with the medical monitor to determine etiology.

10.7.5. Monitoring for Symptoms and Signs of Bleeding and Reductions in Blood Fibrinogen

Blood fibrinogen will be measured as per SoA. In the event of reductions in blood fibrinogen less than LLN, the participant will be evaluated for symptoms of bleeding and the case discussed with the medical monitor. Additional investigations may be required if bleeding occurs or if fibrinogen is abnormal to determine etiology. Participants should be educated to monitor for symptoms of bleeding for example petechiae, bruising, etc.

10.7.6. Monitoring for Exceeding PK Parameters

In the event that any PK criterion specified in Table 9 (Section 4.5) is met in a participant, the actions outlined below will be followed.

- The investigator will assess the clinical status of the participant during direct interaction with the participant at scheduled visits, or via a phone call and/or other communication (as necessary), to determine whether the participant is experiencing any clinical symptoms or signs and/or AEs.
- In the event of an AE, an unscheduled visit may be performed at the discretion of the investigator depending on the nature and severity of the AE. Medical review may include but are not limited to the following:
  - Symptom-directed PE
  - Laboratory tests
  - Vital signs
- In the event of clinically significant laboratory abnormalities, AEs and/or SAEs, standard follow-up and reporting procedures as outlined in the protocol should be followed.

10.8. Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the TOC.

10.8.1. Protocol Amendment 1

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Section # and Name	Description of Change	Brief Rationale
Title page, Section 1.1 Synopsis, Section 4.1 Study Design	Update of "and" to "or" in the title or study design description: A Phase 2a, single dose, open-label, dose-exploration study to assess the PK-PD activity, safety, and tolerability of GSK4532990 in adult participants with NASH **or** suspected NASH	Clarification and for consistency with short title.
Section 1.3 SoA	Addition of Day 1 pre-dose baseline urine sample collection for safety biomarker assessment	Clarification. Collection of baseline sample is required for assessing post-dose biomarkers, if performed.
Section 5.2 Exclusion Criteria	Separated Exclusion Criterion #16 into two separate criteria.	Clarification. No text or content changes resulted in the update.
CCI CCI	CCI	Clarification. Illumina SNP Array is not available for IUO genotyping.
Throughout the protocol	Update of "creatine phosphokinase" and "CPK" to "creatine kinase" and "CK", respectively.	Clarification. Administrative change for consistency.

10.8.2. Protocol Amendment 2

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LIST OF MAIN CHANGES IN THE PROTOCOL AND THEIR RATIONALE

Section # and Name	Description of Change	Brief Rationale
Section 1.2 Study Schemas Figure 1 and Figure 2	Update to the study schema with the addition of new Dose Cohort 4c (for 800 mg treatment arm) figure	To demonstrate schematically the study design change if pre-specified rules are met at Interim Analysis 3 (IA3).
Section 1.3 SoA, Table 4	Addition of a new SoA table for "Post-dose follow up period for Dose Cohort 4a and Dose Cohort 4c only"	New SoA schedule for Dose Cohort 4a and Dose Cohort 4c only if pre-specified rules are met at IA3.
Section 3 OBJECTIVES, ENDPOINTS AND ESTIMANDS Section 9.3.3 Secondary Endpoints/Estimands Analyses	Update of "and" to "or" in the Objectives.	For clarification.
Section 3 OBJECTIVES, ENDPOINTS AND ESTIMANDS, Section 9.3.3 Secondary Endpoints/Estimands Analyses	Addition of note: "If IA3 pre-specified rule has been met, Week 16 will be replaced by Week 20 (for 800 mg Treatment Arm)."	Providing information on addition of new treatment arm if IA3 pre-specified rule has been met.
Section 1.1 Synopsis Section 4.1 Overall Design Figure 3A, 3B	Addition of Dose Cohort 4c to study design.	To provide clarity on study design if pre-specified rules are met at IA3.
Section 1.3 SoA Table 3 Section 4.6 End-of-Study Definition Section 5.1 Inclusion Criteria Section 8.3.4 Clinical Safety Laboratory Tests Section 8.3.5 Pregnancy Testing Section 8.4.6 Pregnancy Section 10.3.5.5 Follow-up of AEs, SAEs, Pregnancies, or Any Other Events of Interest Section 10.4.2 Contraception Guidance	Defining EoS for WOCBP and for all participants except WOCBP.	To provide clarity.
Section 5.1 Inclusion Criteria	Updated text for NASH and ALT, AST and ALP inclusion criteria.	To provide clarity
Section 5.2 Exclusion Criteria	Updated text for prednisone use.	To provide clarity
Section 7.2.1 Participant Addition	Updated text to allow replacement of participants for missing and unevaluable biopsies.	Operational streamlining and to provide clarity
Section 8.4.4.2 Hepatic Events Section 10.7.1.1 Reporting of Events Meeting Liver Monitoring Criteria	Removal of categorization of hepatic events as SAEs.	To be consistent on definition of SAEs.

Section # and Name	Description of Change	Brief Rationale
Section 9.4 Interim Analyses	Addition of text to allow additional safety, tolerability and PK data review.	Operational streamlining
Section 10.1.4 Data Protection	Addition of criterion on data protection.	To harmonize the protocol with the latest protocol template.
Section 10.1.6 Dissemination of Clinical Study Data	Addition of criterion on dissemination of clinical study data.	To harmonize the protocol with the latest protocol template.
Section 10.3.2 Definition of SAE	Updated SAE criterion.	To harmonize the protocol with the latest protocol template text.
Section 10.7.3 Renal Monitoring	Updated text for renal monitoring.	To provide clarity.

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