Clinical Study Protocol	
Study Intervention	AZD2693
Study Code	D7830C00004
Version	5.0
Date	04 Apr 2025
EudraCT / EU CT Number	2022-001629-65 / 2023-509704-14

A Randomised, Double-blind, Placebo-controlled, Multi-centre Phase 2b Study to Evaluate the Efficacy, Safety and Tolerability of AZD2693 in Participants with Non-cirrhotic Non-alcoholic Steatohepatitis (NASH) with Fibrosis Who Are Carriers of the *PNPLA*3 rs738409 148M Risk Allele

Sponsor Name: AstraZeneca AB; AstraZeneca K.K

Legal Registered Address: 151 85 Södertälje, Sweden; 3-1, Ofuka-cho, Kita-ku, Osaka 530-0011, Japan

Regulatory Agency Identifier Number(s)
EudraCT Number: 2022-001629-65
EU CT Number: 2023-509704-14
IND Number: 142897

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Redacted for Public Disclosure

Protocol Number: D7830C00004

Amendment Number: 4.0

Study Intervention: AZD2693

Study Phase: Phase 2b

Short Title: A Randomised Double-Blind Study to Evaluate the Efficacy, Safety and Tolerability of AZD2693 in Participants with Non-Cirrhotic Non-Alcoholic Steatohepatitis (NASH) and Fibrosis Who Are Carriers of the *PNPLA*3 rs738409 148M Risk Allele

Study Physician Name and Contact Information will be provided separately

International coordinating investigator:

PPD
PPD NAFLD Research Centre
PPD
PPD Division of Gastroenterology
University of California at San Diego
ACTRI Building, 1W202
9500 Gilman Drive
La Jolla, CA, 92037-0887

SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
CSP Version 5.0	04-Apr-2025
CSP Version 4.0	01-Jul-2024
CSP Version 3.0	04-Aug-2023
CSP Version 2.0	14-Feb-2023
CSP Version 1.0	13-Sep-2022

CSP Version 5.0 [04-Apr-2025]

This modification is considered to be non-substantial based on the criteria set forth in Regulation (EU) No 536/2014 of the European Parliament because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Modification:

The need for modification arises from the identification and correction of typographical errors present in the previous version. This includes the addition of wording to clarify that the language concerning the worsening of NASH is defined according to health authority guidelines. Additionally, following health authority advice, the significance level has been changed from 0.1 to 0.05, and the confidence interval has been adjusted to 95%.

Summary of Changes:

List of Non-Substantial Modifications

Overall Change	Description of Change	Brief Rationale	Impacted Section Number and Name
Aligned definition of worsening of NASH to health authority guidelines.	Definition of worsening of NASH updated to include 'steatosis' as a criterion.	To align with health authority guidelines.	1.1 (Synopsis) Table 2 (Objectives and Endpoints) 9.4.2.2 (Secondary Endpoint[s])
Clarification of NASH resolution.	Definition of NASH resolution updated to include 'without worsening of fibrosis'.	To clarify definition of NASH resolution.	1.1 (Synopsis) 9.1 (Statistical Hypotheses) 9.2 (Sample Size Determination) 9.4.2.1 (Primary Endpoint[s])

Overall Change	Description of Change	Brief Rationale	Impacted Section Number and Name
Change to significance level and confidence interval.	The significance level has been changed from 0.1 to 0.05, and the confidence interval has been changed from 90% to 95%.	In response to health authority advice.	1.1 (Synopsis) 9.1 (Statistical Hypotheses) 9.2 (Sample Size Determination) 9.4.1 (General Considerations) 9.4.2 (Efficacy) 9.4.2.1 (Primary Endpoint[s])
Multiple testing adjustment clarification.	Clarification that multiple testing adjustment will 'only be applied to the key secondary endpoint' in Section 9.4.2.2 and removal of the sentence regarding multiple testing adjustment from the synopsis.	To provide clarification.	1.1 (Synopsis) 9.4.2.2 (Secondary Endpoint[s])
Unstructured covariance structure model clarification.	Addition that an unstructured covariance structure will be used 'in the model as a first option'.	To provide clarification.	1.1 (Synopsis) 9.4.2.2 (Secondary Endpoint[s])
MRI EDV footnote updated.	Footnote for the MRI EDV was corrected to 'q' from 'r'.	To ensure the correct footnote is referenced in the SoA table.	Table 1 (Schedule of Activities)
MRI-PDFF endpoint updated.	'Liver volume' removed and 'volume corrected HFF' added as an MRI-PDFF endpoint.	For consistency with Section 9.4.2.2.	Table 2 (Objectives and Endpoints)
Correction of exploratory endpoints.	Exploratory endpoints 'liver stiffness', 'HFF', 'volume corrected HFF', and 'liver fat volume' added, and 'no worsening of fibrosis' removed from the resolution of NASH endpoint to align with Table 2 Objectives and Endpoints.	To add previously missed exploratory endpoints and ensure consistency.	9.4.2.2 (Secondary Endpoint[s])
General changes throughout CSP			
Minor revisions.	Minor editorial revisions.	To correct minor typographical errors from the previous CSP version.	Throughout document

TABLE OF CONTENTS

TITLE PAGE 1
SUMMARY OF CHANGES TABLE 3
TABLE OF CONTENTS 5
1 PROTOCOL SUMMARY 10
1.1 Synopsis 10
1.2 Schema 14
1.3 Schedule of Activities 14
2 INTRODUCTION 21
2.1 Study Rationale 21
2.2 Background 21
2.3 Benefit/Risk Assessment 23
2.3.1 Risk Assessment 23
2.3.1.1 Inhibition of *PNPLA3* 23
2.3.1.2 AZD2693 Oligonucleotide Off-target Effect on RAPGEF2 24
2.3.1.3 Thrombocytopenia 24
2.3.1.4 Renal Toxicity 25
2.3.1.5 Liver Toxicity – Transaminase Elevations 25
2.3.1.6 Anti-drug Antibodies 26
2.3.1.7 Injection Site Reactions 26
2.3.1.8 Complement Activation 27
2.3.1.9 Increased Bleeding Risk 27
2.3.1.10 Hypersensitivity and Anaphylactic Reaction 27
2.3.1.11 Pro-Inflammatory Effects 28
2.3.1.12 Study-related Procedures - Liver Biopsy 28
2.3.2 Benefit Assessment 28
2.3.3 Overall Benefit: Risk Conclusion 29
3 OBJECTIVES, ENDPOINTS AND ESTIMANDS 30
4 STUDY DESIGN 35
4.1 Overall Design 35
4.2 Scientific Rationale for Study Design 35
4.2.1 Participant Input into Design 36
4.3 Justification for Dose 36
4.4 End of Study Definition 37
5 STUDY POPULATION 38
5.1 Inclusion Criteria 38
5.2 Exclusion Criteria 41
5.3 Lifestyle Considerations 44
5.3.1 Meals and Dietary Restrictions 44
5.3.2 Alcohol 44

5.3.3 Activity 44
5.4 Screen Failures 44
6 STUDY INTERVENTION 45
6.1 Study Intervention(s) Administered 45
6.1.1 Investigational Products 45
6.2 Preparation/Handling/Storage/Accountability 47
6.2.1 Dose preparation 47
6.2.2 Dose Administration 48
6.3 Measures to Minimise Bias: Randomisation and Blinding 48
6.4 Study Intervention Compliance 49
6.5 Concomitant Therapy 49
6.5.1 Prohibited Concomitant Medications 49
6.5.2 Permitted and Prohibited Therapies for the Management of Type 2 Diabetes Mellitus 51
6.6 Dose Modification 51
6.6.1 Monitoring and Management Plan for Possible DILI 51
6.7 Intervention After the End of the Study 57
7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 57
7.1 Discontinuation of Study Intervention 57
7.1.1 Temporary Discontinuation of Study Intervention 58
7.2 Participant Withdrawal from the Study 58
7.3 Lost to Follow-up 59
8 STUDY ASSESSMENTS AND PROCEDURES 59
8.1 Efficacy Assessments 60
8.1.1 Liver Biopsy-based Histopathology 60
8.1.2 Biomarkers 60
8.1.3 MRI-PDFF/MRE 61
8.2 Safety Assessments 61
8.2.1 Physical Examinations 61
8.2.2 Height, Weight, and Waist Circumference 61
8.2.3 Vital Signs 62
8.2.4 Electrocardiograms 62
8.2.5 Clinical Safety Laboratory Assessments 63
8.2.5.1 Establishing the Baseline ALT Value 65
8.2.6 Other Safety Assessments 66
8.3 Adverse Events and Serious Adverse Events 66
8.3.1 Time Period and Frequency for Collecting AE and SAE Information 67
8.3.2 Follow-up of AEs and SAEs 67
8.3.3 Adverse Events of Special Interest 68
8.3.4 Causality Collection 68
8.3.5 Adverse Events Based on Signs and Symptoms 68

8.3.6 Adverse Events Based on Examinations and Tests 69
8.3.7 Hy's Law 69
8.3.8 Reporting of Serious Adverse Events 69
8.3.9 Pregnancy 70
8.3.9.1 Maternal Exposure 70
8.3.10 Medication Error, Drug Abuse, and Drug Misuse 71
8.3.10.1 Timelines 71
8.3.10.2 Medication Error 71
8.3.10.3 Drug Abuse 71
8.3.10.4 Drug Misuse 71
8.4 Overdose 72
8.5 Human Biological Samples 72
8.5.1 Pharmacokinetics 73
8.5.1.1 Determination of Drug Concentration 73
8.5.2 Immunogenicity Assessments 73
8.5.3 Pharmacodynamics 74
8.5.3.1 Collection of Samples 74
8.5.4 Liver Biopsy 74
8.6 Human Biological Sample Biomarkers 75
8.6.1 Previously Characterised *PNPLA3* I148M Status 75
8.6.2 Collection of Mandatory Samples for Biomarker Analysis 75
8.6.3 Collection of Optional Biomarker Samples 76
8.6.4 Other Study-Related Biomarker Research 76
8.7 Optional Genomics Initiative Sample 77
8.8 Health Economics OR Medical Resource Utilisation and Health Economics 77
8.9 Patient-Reported Outcome Questionnaires 77
9 STATISTICAL CONSIDERATIONS 79
9.1 Statistical Hypotheses 79
9.2 Sample Size Determination 80
9.3 Populations for Analyses 80
9.4 Statistical Analyses 81
9.4.1 General Considerations 81
9.4.2 Efficacy 82
9.4.2.1 Primary Endpoint(s) 83
9.4.2.2 Secondary Endpoint(s) 83
9.4.3 Safety 86
9.5 Interim Analyses 86
9.6 Data Monitoring Committee 86
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 87
11 REFERENCES 157

LIST OF FIGURES

Figure 1 Study Design 14
Figure 2 Flowchart for Monitoring and Management of Possible Hepatocellular DILI in NASH Participants with Normal/Near Normal (< 1.5 x ULN) ALT at Baseline[a] 55
Figure 3 Flowchart for Monitoring and Management of Possible Hepatocellular DILI in NASH Participants with Elevated ALT at Baseline (>1.5 x ULN)[a] 56

LIST OF TABLES

Table 1 Schedule of Activities 14
Table 2 Objectives and Endpoints 30
Table 3 Investigational Products 46
Table 4 Restricted Medications 50
Table 5 Prohibited Medications 50
Table 6 Algorithm for Monitoring and Management of Possible Hepatocellular DILI in NASH Clinical Trials in Patients With Normal or Elevated Baseline ALT (>1.5 x ULN)[a] 51
Table 7 Stopping Criteria for Possible Cholestatic DILI 54
Table 8 Pharmacodynamic Biomarkers 60
Table 9 Laboratory Safety Variables 64
Table 10 Pregnancy and Hormone Testing 66
Table 11 Viral Serology 66
Table 12 Populations for Analysis 80

LIST OF APPENDICES

Appendix A Regulatory, Ethical and Study Oversight Considerations 88
Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting 96
Appendix C Handling of Human Biological Samples 101
Appendix D Optional Genomics Initiative Sample 103
Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law 106

Appendix F Actions in Case of Development of Thrombocytopenia or Uninterpretable Platelet Counts After Administration of ASOs 113
Appendix G Guidance for Definition of Anaphylactic/Hypersensitivity Reactions and Checklist for the Investigator 116
Appendix H Tools for Histological Assessments of Non-alcoholic Steatohepatitis 119
Appendix I Patient-Reported Outcomes Questionnaires 121
Appendix J Coronavirus (COVID-19) Pandemic Guidance 133
Appendix K Alcohol Use Disorder Identification Test (AUDIT) 136
Appendix L Country-specific Requirements 138
Appendix M Abbreviations 139
Appendix N Protocol Version History 143

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title

A Randomised, Double-blind, Placebo-controlled, Multi-centre Phase 2b Study to Evaluate the Efficacy, Safety and Tolerability of AZD2693 in Participants with Non-cirrhotic Non-alcoholic Steatohepatitis (NASH) with Fibrosis Who Are Carriers of the *PNPLA*3 rs738409 148M Risk Allele

Rationale

This Phase 2b study will evaluate the efficacy, safety, and tolerability of AZD2693 in participants with NASH with fibrosis who are homozygous carriers of the *PNPLA3* rs738409 148M risk allele. Those people living with NASH who are also homozygous for the *PNPLA3* 148M risk allele have the highest risk for progression and poor outcomes, including NASH cirrhosis, hepatocellular carcinoma (HCC) and mortality as compared with other target populations (Grimaudo et al 2020, Salameh et al 2016, Unalp-Arida and Ruhl 2020, Walker et al 2020, Wijarnpreecha et al 2021, Xu et al 2015). Thus, these participants are expected to experience the greatest benefit from treatment with AZD2693.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the effect of AZD2693 versus placebo on histological resolution of NASH in participants with non-cirrhotic NASH with fibrosis (and homozygous for the *PNPLA3* rs738409 148M risk allele)	• Proportion of participants achieving NASH resolution [a] without worsening of fibrosis [b] based on histology after Week 52
Secondary	
• To assess the effects of AZD2693 versus placebo on histological fibrosis improvement	• Proportion of participants with at least one stage of liver fibrosis improvement with no worsening of NASH [c] based on biopsy after Week 52
• To assess the effect of AZD2693 versus placebo on ≥ 2-point improvement in NAS	• Proportion of participants with ≥ 2-point improvement from baseline in NAS based on biopsy after Week 52
• To assess the effect of AZD2693 versus placebo on improvement in fibrosis by at least one stage	• Proportion of participants with improvement in fibrosis by at least one stage based on biopsy after Week 52

Objectives and Endpoints

Objectives	Endpoints
Safety	
• To assess safety and tolerability of AZD2693 compared with placebo	• Safety and tolerability will be evaluated in terms of AEs, vital signs, ECG, and clinical and laboratory evaluation including platelet count

[a] Resolution of NASH as defined by the NASH CRN as "any grade of steatosis, no ballooning, and only minimal (grade 1) lobular inflammation"

[b] Worsening defined by an increase of at least one stage of the Kleiner fibrosis classification

[c] Worsening defined as an increase of at least one stage of either lobular inflammation or hepatocyte ballooning or steatosis according to NASH CRN criteria

AE, adverse event; CRN, Clinical Research Network; ECG, electrocardiogram; NAS, Non-alcoholic fatty liver disease Activity Score; NASH, non-alcoholic steatohepatitis.

For Tertiary/Exploratory objectives and endpoints, see Section 3 of the protocol.

Overall Design

This is a Phase 2b, 52-week randomised, double-blind, placebo-controlled, multi-centre, multinational trial comparing once monthly subcutaneous (SC) administration of AZD2693 in participants with non-cirrhotic NASH (F2-F3) who are homozygous for the *PNPLA3* rs738409 148M risk allele.

This Phase 2b study is planned to evaluate 2 different doses (25 and 50 mg) with corresponding injection volumes of placebo.

The randomisation ratio of homozygous participants receiving AZD2693 or placebo will be 2:1.

For more information on the dosing rationale, see Section 4.3 of clinical study protocol (CSP).

Disclosure Statement

This is a Phase 2b, 52-week randomised, double-blind, placebo-controlled, multi-centre, multinational trial comparing once monthly SC administration of AZD2693 versus placebo in participants with non-cirrhotic NASH (F2-F3) who are homozygous carriers of the *PNPLA3* rs738409 148M risk allele.

Number of Participants

The study will randomise approximately 180 participants.

Intervention Groups and Duration

The study includes a screening period of up to 10 weeks (inclusive of 2-week early genotyping assessment) followed by randomisation, 52-week treatment period and about 12-week safety follow-up period.

Data Monitoring Committee

An independent Safety Monitoring Committee (iSMC) will perform continuous safety monitoring according to the iSMC charter. Details of the continuous safety monitoring will be specified in the iSMC charter. The role and the primary responsibilities of the iSMC members will be described in the committee charter.

The study will engage an independent clinical event adjudication (CEA) committee to independently review, interpret and adjudicate potential cardiovascular (CV) and liver events experienced by the participants. The CEA committee members will not have access to individual treatment codes for any participant. The precise responsibilities and procedures applicable for CEA will be detailed in the CEA charter.

Appendix A 5 of CSP provides more details regarding the remit of the committees.

Statistical Methods

Sample Size

About 60 participants in each AZD2693 dose arm and about 30 participants in two separate placebo arms will provide more than 90% power for the test of each dose versus placebo to detect a difference of 35% in NASH resolution without worsening of fibrosis assuming a response rate to placebo of 20%. The calculations assume a 2-sided alpha level of 0.05.

Primary Efficacy Analyses

The primary objective is to demonstrate superiority of AZD2693 compared to placebo on the resolution of NASH without worsening of fibrosis after Week 52 in participants homozygous for the *PNPLA3* rs738409 148M risk allele.

To support the primary objective, the primary endpoint is

- The resolution of NASH without any worsening of fibrosis (yes/no).
  - The resolution of NASH is defined as a ballooning score of 0, inflammation score of 0 to 1, and steatosis score of any degree (from 0 to 3), as assessed by NASH Clinical Research Network (CRN)/NASH Activity Score (NAS).
  - Worsening of fibrosis is defined as an increase in the NASH CRN fibrosis score.

The summary measure for the primary endpoint will be proportion of responders. The primary endpoint will be analysed using a Cochran-Mantel-Haenszel test with stratification by type 2 diabetes mellitus (T2DM) presence and F2 or F3 fibrosis stages based on the full analysis set population. The treatment effects will be summarised by the difference in proportions, 95% confidence interval, and p-value.

Secondary Efficacy Analyses

For participants homozygous for the *PNPLA3* rs738409 148M risk allele, secondary endpoints are:

- Key secondary: At least one stage of liver fibrosis improvement with no worsening of NASH (yes/no) after 52 weeks (worsening defined as an increase of at least one stage of either lobular inflammation or hepatocyte ballooning or steatosis according to NASH CRN criteria)
- Improvement in fibrosis by at least one stage based on biopsy after Week 52
- $\geq$ 2-point improvement in NAS after 52 weeks

Binary endpoints will be analysed using the same Cochran-Mantel-Haenszel approach as for the primary endpoint. Where applicable, the analyses of the change from baseline variables will each utilise a repeated measures model with fixed effects of baseline value, presence of T2DM, fibrosis stage (F2/F3), week, treatment, the interaction of treatment and week. An unstructured covariance structure will be used in the model as a first option. No explicit imputation of missing values will be made for these repeated measures models. Participants with missing final histology data will be assumed to be non-responders.

Safety

Safety data will be summarised descriptively and will not be formally tested.

All safety data will be presented in the data listings. In addition, renal safety biomarkers, platelet count and liver biochemistry parameters (alanine aminotransferase, aspartate aminotransferase, bilirubin) will be presented graphically by treatment (dose level of AZD2693, and pooled placebo).

Adverse events (AEs) will be coded using the most recent version of Medical Dictionary for Regulatory Activities vocabulary. AEs will be presented for each treatment group by System Organ Class and/or Preferred Term, covering number and percentage of participants and number of events where appropriate.

The summaries will include AEs, serious AEs, and AEs leading to discontinuation of study intervention. AEs by severity and causally related AEs will also be presented.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination compared to the baseline assessment will be reported as an AE.

1.2 Schema

Figure 1 Study Design



Bx, biopsy; HMZ, homozygous; N, number; NASH, non-alcoholic steatohepatitis; R, randomisation; sc, subcutaneous

1.3 Schedule of Activities

Table 1 Schedule of Activities

Study Phase	Screening (10 weeks)		Study Intervention Period (52 weeks)																			Follow-up Period (12 weeks)				
Visit	1	2[d]	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	ED[e]	CSP Section
Study week	-10 to -8	-7 to -1	1	2	4	6	8	10	12	14	16	20	24	26	28	32	36	40	44	48	52	54	58	64		
Visit window (days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3		
Informed consent	X[a]	X																								5.1

Study Phase	Screening (10 weeks)		Study Intervention Period (52 weeks)																			Follow-up Period (12 weeks)				
Visit	1	2 [d]	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	ED [e]	CSP Section
Study week	-10 to -8	-7 to -1	1	2	4	6	8	10	12	14	16	20	24	26	28	32	36	40	44	48	52	54	58	64		
Visit window (days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3		
Eligibility criteria	X	X	X																							5.1, 5.2
PNPLA3 genotyping [a,b,d]	X [c]																									5.1, 8.6.1, 8.6.2
Demography	X																									5.1
Height		X																								8.2.2
Weight, waist, BMI		X	X		X		X		X		X	X	X		X	X	X	X	X	X	X			X	X	8.2.2
Medical history		X																								5.1, 5.2
Drugs of abuse [f], alcohol		X																								5.2
Hep B, Hep C, HIV		X																								8.2.6, 5.2
Pregnancy		X	X		X		X		X		X	X	X		X	X	X	X	X	X	X			X	X	5.2, 8.2.6, 8.3.9

Study Phase	Screening (10 weeks)		Study Intervention Period (52 weeks)																			Follow-up Period (12 weeks)				
Visit	1	2[d]	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	ED[e]	CSP Section
Study week	-10 to -8	-7 to -1	1	2	4	6	8	10	12	14	16	20	24	26	28	32	36	40	44	48	52	54	58	64		
Visit window (days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3		
Trial material																										
Randomisation			X																							6.3
Enrolment in IRT/RTSM[aa]	X	X																								
IP administration and drug accountability			X		X		X		X		X	X	X		X	X	X	X	X	X	X					6.1, 6.2
Safety																										
AEs	X[g]	X[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3
Physical exam		X	X	X[h]	X[h]		X[h]		X[h]		X[h]	X[h]	X[h]		X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X			X	X	8.2.1
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.5
Vital signs		X	X	X	X		X		X		X	X	X		X	X	X	X	X	X	X			X	X	8.2.3
12-lead pECG		X	X		X				X				X				X				X			X	X	8.2.4
Clinical safety labs	X[i]	X[j]	X[x]	X	X	X[k]	X	X[k]	X	X[kx]	X	X	X		X	X	X	X	X	X	X		X[y]	X	X	8.2.5

Study Phase	Screening (10 weeks)		Study Intervention Period (52 weeks)																			Follow-up Period (12 weeks)				
Visit	1	2[d]	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	ED[e]	CSP Section
Study week	-10 to -8	-7 to -1	1	2	4	6	8	10	12	14	16	20	24	26	28	32	36	40	44	48	52	54	58	64		
Visit window (days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3		
Injection site reaction			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.2.6
ADA			X	X	X						X		X		X			X			X			X	X	8.5.2
Pharmacokinetics																										
Plasma for PK			X[l]	X[m]	X[n]	X[m]					X[n]		X[l,n]	X[m]	X[n]			X[n]			X[n]	X[o,m]		X[m]		8.5.1
Efficacy																										
Liver biopsy[p]		X																				X			X[q]	8.5.4
MRI-PDFF, MRE[r]		X												X								X[s]			X[q]	8.1.3
Inflammatory biomarkers			X[t]										X[t]								X[t]	X			X	8.6.2
Exploratory end-point biomarkers		X[z]	X[t]		X[t]				X[t]				X[t]								X[t]	X[o]		X		8.6.2 Table 8
Patient-Reported Outcomes[u]																										
NASH-CHECK, SF-36, PGIS			X[u]										X								X				X	8.9

Study Phase	Screening (10 weeks)		Study Intervention Period (52 weeks)																		Follow-up Period (12 weeks)				
Visit	1	2 [d]	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	ED [e]	CSP Section
Study week	-10 to -8	-7 to -1	1	2	4	6	8	10	12	14	16	20	24	26	28	32	36	40	44	48	52	54	58	64		
Visit window (days)				±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3		
Participant interviews [v]		X																			X				X	8.9
Additional assessments																										
Exploratory blood sample for cell free DNA			X		X																X					8.1.2 8.6.2
Optional: Biomarkers future research [w]			X [t]		X [t]				X [t]				X [t]								X [t]			X	X	8.6.3
Optional: Genomics Initiative, exploratory genetic sample [w]			X																							8.7, Appendix D

[a] Participants must first consent to a genotyping assessment to determine eligibility; if deemed eligible, they must provide an additional signed ICF to participate in the study.

[b] Participants may proceed to other screening assessments as soon as they are deemed eligible based on their central genotyping results.

[c] Participants who have already submitted bloods/buccal swabs for genotyping at sites participating in the optional "Screening Study in Participants at risk or confirmed NASH" are not required to submit further genotyping samples at Visit 1 in this study.

[d] Screening (inclusive of genotyping assessment) can be split into several visits over 10 weeks. Up to two weeks are recommended for Visit 1 screening. However, the time window for the Genotyping visit may be adjusted to accommodate delays (>2 weeks) in receipt of the genotyping results (due to failed/repeat test) and/or situations when patients cannot attend the visit assigned in the recommended timeframe as long as the 10-week screening window is not exceeded. Sites are encouraged to perform the screening (V1 and V2) assessments as soon as possible within the 10-week screening window.

[e] Performed in the event of early discontinuation of study intervention or withdrawal from study prior to Week 54 (Visit 22).

[f] Sites may use their standard panel for urine testing of drugs of abuse (investigator discretion may be used if positive for prescribed medication[s] or legal substances).

[g] SAEs are collected from the time of first signing consent (starting at Visit 1). AEs are collected from the time of randomisation (Visits 3-24).

[h] Brief physical examination

[i] Liver enzymes only (AST, ALT, TBL).

[j] ALT values must be collected at least 2 weeks apart within the 10-week screening timeframe.

[k] Platelet count and ALT only.

[l] Blood sampling for plasma quantification of AZD2693 to be taken 2 hours post-dose on Visit 3 and Visit 13. Note: both pre-dose and post-dose samples are collected at Visit 13.

[m] Blood sampling at Visits 4, 6, 14, 22 and 24 may be collected at any time of day during the visit. Time of sample collection should be recorded.

[n] Blood sampling for plasma quantification of AZD2693 to be taken pre-dose on Visits 5, 11, 13, 15, 18, and 21. Note: both pre-dose and post-dose samples are collected at Visit 13.

[o] Only for biopsy visit. No sampling required when doing MRI-PDFF/MRE assessment.

[p] For participants without a historical biopsy (acceptable within 6 months prior to randomisation), the liver biopsy at screening (Visit 2) will be scheduled after all other screening procedures, once it has been confirmed that the participant meets all other eligibility criteria and that necessary safety laboratory assessments are available. In the event of issues with historical biopsies and central reading, the participants may be asked to take a fresh biopsy sample; the screening window of Visit 2 can be extended by up to 4 weeks in total.

[q] Biopsy and MRI/MRE should be conducted as part of the EDV activities only in participants who have received study intervention for at least 36 weeks.

[r] This assessment is to be performed at selected investigational sites with MRI-PDFF/MRE capabilities or affiliated to facilities with MRI-PDFF/MRE capabilities in approximately 26 participants per arm who are homozygous for the *PNPLA3* 148M risk allele. MRI-PDFF/MRE should be performed with at least 4 hours of fasting and within a ± 2-hour window from the baseline scan.

[s] Some sites may not have the capacity to perform both liver biopsy and MRI-PDFF/MRE at the same location; in this case, Visit 22 may be split into multiple visits to accomplish all procedures.

[t] Samples to be taken pre-dose administration.

[u] Patient-reported outcome questionnaires should be conducted before other assessments to avoid bias. Baseline assessments at Visit 3 must be completed before treatment initiation. For Visits 13 and 21, these can be conducted within ±7 days.

[v] Participant qualitative interviews will only be conducted for participants enrolled in the United States (might be expanded to other countries as well). The interviews will be conducted by phone. The first interview will occur at baseline (prior to first dose within screening period) after consent is signed. Vendors conducting interviews will be notified of the identification of an eligible participant and the date of scheduled first dose as soon as possible. Best efforts will be made to schedule all interviews within the windows allowed.

[w] Optional blood sampling will be collected only if participants consent to optional components of the study in the ICF relating to sample for future biomarker research and/or samples for genetic research.

[x] Including GLDH.

[y] ALT, AST and GGT only

[z] Of the exploratory biomarkers listed in Section 8.1.2 Table 8, only ELF score will be measured at SCR Visit 2

[aa] For participants resulting eligible at genotyping, an additional transaction at V2 has to be performed on the same day the ICF V2 is signed in order to proceed with Screening V2 assessments.

Note: All blood samples are required fasting for 8 hours except the following samples which are allowed without fasting

- Blood safety samples for platelets (Visit 6 and 8), liver enzymes (AST, ALT and TBL at Visit 1; ALT at Visit 6, 8; and ALT, AST and GGT at Visit 23)
- PNPLA3 genotyping samples (Visit 1) and optional exploratory genetic samples (Visit 3)
- Post IP administration for PK sampling (Visit 3 and Visit 13)
- All visits are non-residential (ie, no on-site, overnight stay).

ADA, anti-drug antibody; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase/transaminase; BMI, body mass index; CSP, clinical study protocol; ED, early discontinuation; EDV, early discontinuation visit; ELV, Enhanced Liver Fibrosis; EOT, end of treatment; GGT, Gamma-glutamyl transferase; GLDH, glutamate dehydrogenase; Hep, hepatitis; HIV, human immunodeficiency virus; ICF, informed consent form; IP, investigational product; IRT/RTSM, interactive response technology/randomisation and trial supply management; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging–based proton density fat fraction; NASH, non-alcoholic steatohepatitis; NASH-CHECK, Patient-Reported Outcome Measure for Non-Alcoholic Steatohepatitis; pECG, paper-based electrocardiogram, PCR, polymerase chain reaction; PK, pharmacokinetics; PGIS, Patient-Reported Outcome Measure for Patient Global Impression of Severity; SAE, serious adverse event; SCR, screening visit; SF-36, Patient-Reported Outcome Measure for General Health Status; TBL, total bilirubin.

2 INTRODUCTION

AZD2693 is a *PNPLA3*-targeted, GalNAc-conjugated ASO that inhibits *PNPLA3* mRNA and subsequent protein expression in the liver. AZD2693 may provide a novel, personalised treatment option for *PNPLA*3 I148M patients with NASH.

2.1 Study Rationale

The objective of this Phase 2b study is to evaluate efficacy, safety, and tolerability of AZD2693 in participants with NASH with fibrosis who are homozygous for the *PNPLA3* rs738409 148M risk allele. Those with NASH who are homozygous for the *PNPLA3* 148M risk allele have the highest risk for progression and poor outcomes, including NASH cirrhosis, HCC and mortality as compared with other target populations (Grimaudo et al 2020, Salameh et al 2016, Unalp-Arida and Ruhl 2020, Walker et al 2020, Wijarnpreecha et al 2021, Xu et al 2015). Thus, these participants are expected to experience the greatest benefit from treatment with AZD2693.

2.2 Background

NASH and Patient Burden

Non-alcoholic steatohepatitis (NASH) is part of the spectrum of liver diseases known as NAFLD. NAFLD is the most common cause of chronic liver disease in Western industrialised countries, with an estimated prevalence of approximately 6% to 35% worldwide (Bellentani 2017, Younossi et al 2016). NASH is the progressive form of the disease with a prevalence of approximately 2% to 3% in the general population. It can lead to cirrhosis and complications with high morbidities and mortality, including HCC and end-stage liver disease (Bellentani et al 2010). NASH is expected to become the leading indication for liver transplantation over the next decade and is an important aetiology driving the burden of HCC (Cholankeril et al 2017, Pais et al 2016, Wong et al 2014).

Approximately 25% to 35% of patients with NASH develop liver fibrosis, which is associated with poor long-term outcomes (Angulo et al 2015, Mishra and Younossi 2012).The severity of hepatic fibrosis is an important predictor of liver-related mortality in NAFLD (Chalasani et al 2018, Younossi et al 2018). Several factors have been shown to increase the risk of liver fibrosis progression to cirrhosis including presence of comorbid T2DM, increasing age, hypertension, and high BMI, along with genetic factors including *PNPLA3* I148M (Angulo 2007, Angulo et al 2015). An SNP rs738409:C>G results in an aminoacidic substitution of an M for an I at position 148 (p.I148M) of the PNPLA3 protein (Romeo et al 2008). Evidence shows that an SNP (rs738409) in the sequence of the human *PNPLA3* gene is a key genetic determinant of hepatic fat content and poor NAFLD outcomes: *PNPLA3* 148M (Romeo et al 2008, Unalp-Arida and Ruhl 2020, Grimaudo et al 2020).

In the US, the highest proportion of NAFLD is in Hispanic/Latino populations, whilst the lowest burden is observed in Black/African American populations (Iqbal et al 2019, Rich et al 2018). The ethnic distribution of the *PNPLA3* 148M allele mirrors the varied ethnic propensity to develop NAFLD (eg, 49% in Hispanic [propensity 45%]; 23% in European American [propensity 33%]; and 17% in African American populations (Kallwitz et al 2019, Romeo et al 2008). Additionally, Hispanic/Latino, Chinese and Japanese populations have higher proportions *PNPLA3* according to a sponsor's analysis.

To date, there are no globally approved treatments for NASH or first-line therapies for NAFLD. Treatment approaches for NASH focus on lifestyle modification to achieve weight loss and reduce comorbidities, including diabetes, hyperlipidaemia and hypertension (Burdick et al 2014, Burel et al 2016, Chalasani et al 2018, Younossi et al 2018). Once NASH progresses to cirrhosis and end-stage liver disease, the only option currently available is liver transplantation.

AZD2693: Nonclinical and Clinical Evidence

AZD2693 is a *PNPLA3*-targeted, GalNAc-conjugated ASO that inhibits *PNPLA3* mRNA and subsequent protein expression in the liver. AZD2693 may provide a novel, personalised treatment option for participants with NASH who are homozygous carriers of the *PNPLA3* 148M risk allele.

Preclinical Evidence

In a non-clinical proof of concept study, silencing of mouse hepatic *PNPLA3* mRNA and protein expression using a GalNac-conjugated ASO targeting mouse *PNPLA3* mRNA decreased liver steatosis, inflammation, and fibrosis in *PNPLA3* I148M knock-in mice fed a NASH-inducing diet (Linden et al 2019).

Clinical Evidence

Safety, tolerability, and PK of AZD2693 have been investigated at single doses of 2 mg to 110 mg in the Single Ascending Dose (SAD) study, which also included 2 cohorts of Japanese and one cohort of Chinese healthy volunteers. In addition, the safety, tolerability, PK and PD (reduction of liver fat assessed by MRI-PDFF) of 25 mg and 50 mg of repeated monthly doses of AZD2693 have been investigated in a global Multiple Ascending Dose (GMAD) study in presumed NASH (F0-F3) participants homozygous carriers of the PNPLA3 148M risk allele, with one cohort of 25 mg in heterozygous PNPLA3 148M risk allele participants. An 80 mg cohort in PNPLA3 148M homozygous participants is ongoing in parallel with Phase 2b (to generate additional safety exposure coverage and provide confirmation of $\geq$ 95% predicted mRNA knockdown). A Japan multiple ascending dose (JMAD) study has evaluated the safety, tolerability, and PK of repeated monthly doses of AZD2693 25 mg, 50 mg and 80 mg (the highest dose completed in both a Japanese and non-Asian healthy volunteer cohort).

An interim analysis of the GMAD PD effect of AZD2693 on LFC assessed by MRI-PDFF (n = 15 on active; n = 10 on placebo) demonstrate placebo-corrected reduction in LFC of approximately 14% and 18% (least square means) for 25 mg and 50 mg doses in homozygous study participants, respectively, at week 12. The dose-dependent reduction in LFC supports PNPLA3 mRNA target knockdown (88% and 93%) and demonstrates Proof of Principle in presumed NASH participants homozygous for PNPLA3 148MM.

AZD2693 has been generally well tolerated and the majority of the AEs reported have been mild or moderate in intensity. To date, 1 SAE (appendicitis in the SAD study) and no AEs have been reported leading to discontinuation of study drug. There were no cases of thrombocytopenia, renal toxicity, impaired blood coagulation, complement activation, hypersensitivity/anaphylactic reaction, or flu-like reactions. The majority of ISRs were mild and transient.

Data from the MAD interim analysis suggest a low-level increase in mean absolute ALT. Complete follow up data from the heterozygote cohort add one additional participant with low-level increase in mean absolute ALT such that four participants (one healthy Chinese volunteer at the 110 mg dose in the SAD study, one Japanese healthy volunteer in the 80 mg cohort in the JMAD study, and two presumed NASH participants in the GMAD study, one in the 50 mg homozygous cohort and one in the 25 mg heterozygous cohort) had ALT of ≥ 3 and $<5 \times$ ULN, with no increase in TBL and no symptoms. Frequent ALT monitoring and DILI detection algorithm modifications in the Phase 2b study will provide data to characterize this observation.

Further information about AZD2693 is provided in the Investigator's Brochure.

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

More detailed information about the known and expected benefits and potential risks of AZD2693 can be found in the Investigator's Brochure.

Specific risks identified based on risks observed in some oligonucleotide programs, and potential risks based on the mechanism of action of AZD2693, are described below.

2.3.1.1 Inhibition of *PNPLA3*

AZD2693 is a GalNAc-conjugated ASO designed to specifically inhibit *PNPLA3* mRNA expression in the liver, utilising the ASGR for enhanced uptake to hepatocytes versus non-parenchymal cells, enabling the use of a lower dose when administered. *PNPLA3* is a triglyceride and retinyl hydrolase predominantly expressed in the liver and retina (Pingitore and Romeo 2019). Nonclinical data support the safety of *PNPLA3* suppression: knockdown of *PNPLA3* was well tolerated in murine models; and no abnormal phenotype was

reported for PNPLA3 knock-out mice (Basantani et al 2011). In contrast to the association of *PNPLA3* and hepatic steatosis, *PNPLA3*-dependent retinol (vitamin A1) metabolism is less understood. Vitamin A1 is converted by the retinal pigment epithelium into 11-cis-retinal, a key factor of the visual cycle in photoreceptor cells.

PNPLA3 mRNA have the highest expression in human retina followed by liver, adrenals, kidney, skin, and fat cells (Pirazzi et al 2014). In monkeys administered once weekly doses ranging from 0.5 to 15 mg/kg/week), there were no detectable levels of unconjugated AZD2693 in secondary tissues (spleen, adipose, heart, brain, ovary, testes, or thyroid) in the low-dose group, and the levels detected in the mid- and high-dose groups were substantially lower than those detected in liver and kidney. Mouse-active ASOs administered SC at 1 and 5 mg/kg to mice show no knockdown of *PNPLA3* in the eye. Non-conjugated ASOs of same chemistry and design as AZD2693 show no exposure (IHC staining) of NHP retina after 26 weeks of weekly SC administration at 32 mg/kg. It is not known how knockdown of *PNPLA3* may impact vision. Based on the available data in the AZD2693 clinical study programme, no effect on s-retinol or night blindness has been observed.

Risk management: S-retinol and retinol binding protein will be monitored every month.

2.3.1.2 AZD2693 Oligonucleotide Off-target Effect on RAPGEF2

Risks associated with knockdown of Rapgef2 mRNA were assessed in 1) non-clinical murine reproductive toxicity studies using a specific ASO targeting Rapgef2 mRNA; 2) the pivotal 3-month and chronic 9-month toxicity studies with cynomolgus monkey, and 3) a 14-day in vitro study in human hepatic spheroids. No effects were observed. Based on the available data, AZD2693 is not expected to cause clinically relevant off-target effects on RAPGEF2. A detailed description of non-clinical studies for AZD2693 is provided in the Investigator's Brochure.

Risk management: Regular AE monitoring.

2.3.1.3 Thrombocytopenia

Severe, reversible thrombocytopenia has been observed in a few unique ASO programs in clinical studies. Mild self-limited reductions in platelet counts that have typically resulted in platelet levels above the LLN have been observed in some programs (Crooke et al 2017). No significant alterations were observed in AZD2693 GLP toxicology studies. Based on the available data in the AZD2693 clinical study programme, there are no confirmed platelet count $< 100 \times 10^9$/L or observations of mild platelet count reductions.

Risk management: Participants with a confirmed platelet count < LLN or bleeding disorders, including known platelet dysfunction disorders, will not be included in this study. Platelet count levels will be monitored, initially every other week for 4 months, and thereafter every month. If platelet count drops a confirmed value of $< 100 \times 10^9$/L, or $< 150 \times 10^9$/L

but > 100 × 10^9/L with > 30% reduction from baseline, participants will be more frequently monitored according to Appendix F. For individual stopping criteria see Section 7.1.

2.3.1.4 Renal Toxicity

The kidney is an oligonucleotide high-uptake tissue. Acute kidney injury in the form of acute tubular necrosis after single or a few repeated doses has rarely been observed with some ASOs. Acute kidney injury was not predicted from the non-clinical studies (van Poelgeest et al 2013, van Poelgeest et al 2015, van Meer et al 2017). No significant renal alterations were observed in AZD2693 GLP toxicology studies. In the 3-month monkey study, the overall mean urine recovery was less than 3% at doses up to 15 mg/kg/week. In the SAD study (D7830C00001), the fraction of the administered dose (conjugated AZD2693) excreted unchanged in urine was negligible (< 1%) in the 72 hours post-dose period. Based on the available data in the AZD2693 clinical study programme using traditional measures, as well as a safety composite biomarker panel to aid in the detection of kidney tubular injury in Phase 1 trials in healthy volunteers (Foundation for the National Institutes of Health 2019), there is no indication of acute renal impairment/renal toxicity with AZD2693.

Risk management: Participants with historical or pre-existing renal disease marked by eGFR < 40 mL/min/1.73 m^2 will not be included in the study. Renal function will be monitored through assessment of s-Cr, eGFR, urinary albumin and urinary protein. Individual stopping criteria are applied in the study (see Section 7.1).

2.3.1.5 Liver Toxicity – Transaminase Elevations

Liver is an oligonucleotide high-uptake tissue (Hung et al 2013). Oligonucleotide treatment may cause transient transaminase elevations in mice, monkeys and humans at therapeutic exposures (Burdick et al 2014, Hagedorn et al 2013, Hildebrandt-Eriksen et al 2012, Santos et al 2015, Kleiner et al 2014). AZD2693 is a GalNAc-conjugated ASO utilising the ASGR to enhance uptake by hepatocytes. Therapeutic exposures of AZD2693 in non-clinical GLP toxicology studies were well-tolerated.

In pivotal murine and primate toxicity studies, weekly dosing of AZD2693 up to 6 months in mice and 9 months in monkeys were associated with dose-dependent increases in liver enzymes (ALT/AST in mice and glutamate dehydrogenase in monkeys). In murine models, these changes were associated with Kupffer cell vacuolation, pigmented macrophages, histiocytic infiltration, and single cell necrosis at a high dose level of 100 mg/kg/week. Increased liver weight was also observed in the cynomolgus monkey, but the histopathological changes in the liver were restricted to minimal/mild mononuclear cell infiltration. Changes in the liver enzymes and microscopic findings in the liver are consistent with an adaptive response to the high hepatocellular uptake of ASOs (Frazier 2015).

A low-level increase in mean absolute ALT have been observed in the ongoing MAD studies. In the full clinical study programme, increases in ALT ≥ 3 x ULN and < 5 x ULN have been

seen in 4 participants (see Section 2.2 for details). No increase in total bilirubin has been observed in any of these 4 participants and no clinical signs or symptoms have been associated.

Risk management: Participants with a confirmed liver safety biomarker value outside the pre-defined criteria specified in exclusion criteria, history of liver transplant, current placement on a liver transplant list, liver disease of other aetiologies or a history of cirrhosis and/or hepatic decompensation will not be included in the study.

Liver transaminases (ALT/AST), ALP, GGT and GLDH will be monitored repeatedly. Individual stopping criteria are applied in the study (see Section 7.1). An iSMC will continuously review safety data during the study. AstraZeneca will use an algorithm for monitoring and management of possible drug-induced liver injury in participants with normal or elevated baseline ALT, based on the IQ DILI Initiative consensus guideline, illustrated in Table 6. Liver events will be adjudicated by an independent blinded adjudication committee.

2.3.1.6 Anti-drug Antibodies

There is a potential risk for ADA formation based on observations of decreasing systemic clearance upon repeat administration in the 9-month monkey toxicity study. Emergence of ADAs has been observed in some participants after repeated oligonucleotide treatment. No association of ADAs with loss of efficacy or safety has been seen with ASOs. ADA results from ongoing AZD2693 studies are not yet available.

Risk management: Autoimmune reactions are monitored through regular AE reporting. ADA samples will be collected and assessed in the study. In the event of a suspected anaphylactic reaction, additional ADA samples will be collected. Guidance on the definition of an anaphylactic reaction and the action plan that needs to be followed with regards to ADA sampling is presented in Appendix G.

2.3.1.7 Injection Site Reactions

As with any exogenous substance, injection site reactions may occur as a response to the SC injection of AZD2693. Possible risks associated with SC administration are redness, swelling, pain, induration and sometimes infection at the administration site. Although observed for some ASOs, injection site reactions are not generally a clinical problem for newer generation ASOs (Crooke et al 2018). Based on the available data in the AZD2693 clinical study programme, the majority of reported ISRs were mild, and there have been no discontinuations due to ISRs.

Risk management: Injection sites will be monitored for injection site reactions.

2.3.1.8 Complement Activation

Complement activation has been observed in primates after ASO administration and appears to be directly driven by plasma concentration (Crooke et al 2016). Higher complement Bb concentrations were noted in males and females on Day 85 following dosing; these findings were not associated with any changes in other complement parameters or histopathology. However, in the 9-month primate toxicity study, increases in complement Bb concentrations were accompanied in some animals with adverse clinical signs, leading to premature euthanasia. Histopathological findings included minimal to marked mural and/or perivascular arterial inflammation in multiple tissues.

The key factor involved in the pathogenesis of this type of vascular injury in monkeys is believed to be complement activation. This is a widely recognised complication of antisense therapy in monkeys and is related to direct inhibition of negative regulators (specifically Factor H) of the alternative complement pathway (Crooke et al 2016). Non-human primates are particularly susceptible to complement-related arterial inflammation, whereas there is no evidence of equivalent complement activation occurring in humans or other species (Kato et al 2012, Engelhardt et al 2015). Further details are included in the IB. Based on the available data in the AZD2693 clinical study programme, no changes in C5a or Bb have been observed.

Risk management: Monitoring of complement activation (C5a, Bb). Subcutaneous administration reduces the risk for high C_{max} compared to infusion.

2.3.1.9 Increased Bleeding Risk

Increases in APTT, in the absence of clinical or pathological sequelae, have been observed with ASOs (Burel et al 2013; Henry et al 1997). Transient prolongation of APTT has been described in humans and was observed to correlate with maximum ASO concentration at the end of IV infusion (Sewell et al 2002). There were no treatment related changes in any coagulation parameters in the non-clinical toxicology studies for AZD2693. Based on the available data in the AZD2693 clinical study programme, no change in APTT or PT has been observed.

Risk management: APTT and PT will be assessed repeatedly over the study period. AZD2693 is administered SC, which reduces the risk for high C_{max} compared to IV administration.

2.3.1.10 Hypersensitivity and Anaphylactic Reaction

As with any foreign biological agent, administration of AZD2693 may induce hypersensitivity reactions. These acute reactions are important because they may be severe but are considered rare.

Risk management: Participants with known history of hypersensitivity reactions will be excluded from the study. Participants in clinical studies of AZD2693 will be closely

monitored during and after administration of study intervention for hypersensitivity reactions. Severe hypersensitivity reactions should be managed according to standard clinical practice; medical equipment and well-trained staff must be available to treat acute anaphylactic reactions at all sites. If an anaphylactic or other serious allergic reaction occurs, administration of AZD2693 should be stopped immediately and appropriate therapy administered. Further guidance on hypersensitivity and anaphylactic reactions is presented in Appendix G.

2.3.1.11 Pro-Inflammatory Effects

In pivotal murine and primate toxicity studies, weekly dosing of AZD2693 for up to 6 months in mice and 9 months in monkeys was associated with histopathological changes considered to be related to the pro-inflammatory effects elicited by ASOs. It is the most common hybridisation-independent effect associated with oligonucleotide administration and believed to be a consequence of cellular activation and subsequent cytokine and chemokine release.

Risk management: Flu-like symptoms (chills, myalgia, arthralgia, feeling hot and increased body temperature) are usually mild and self-limiting; symptomatic treatment may relieve more severe manifestations. Participants will be monitored for flu-like symptoms. Additionally, hs-CRP, albumin, complement C3 and C5 (Total, not activated complement), Bb, fibrinogen, MCP-1, and IL-6 will be assessed, allowing for early detection of an inflammatory process. Guidance on the definition of an anaphylactic reaction and the action plan that needs to be followed is presented in Appendix G. Major CV events will be adjudicated by an independent blinded adjudication committee.

2.3.1.12 Study-related Procedures - Liver Biopsy

The most common risks associated with liver biopsy are mild pain and minimal bleeding at the procedure site. Rare complications of liver biopsy include major bleeding (0.1%) and death (0.01%) (Nalbantoglu and Brunt 2014).

Risk management: Each investigator or designee who obtains a liver biopsy must be experienced and qualified to perform the procedure. In participants with contraindications to the procedure, evidence of hepatic decompensation and/or coagulopathy, a biopsy should not be performed. Relevant laboratory parameters (eg, INR and platelet count) will be checked prior to the procedure, and the use of drugs that may affect coagulation (eg, warfarin, heparin, aspirin and antiplatelets, and NSAIDs) will be assessed. For further information, see Section 8.5.4.

2.3.2 Benefit Assessment

AZD2693 is a PNPLA3- targeted, GalNAc-conjugated ASO that inhibits *PNPLA3* mRNA and subsequent protein expression in the liver. AZD2693 may provide a novel, personalised treatment option for participants with NASH who are carriers of *PNPLA3* 148M. Participants with NASH who are homozygous for the *PNPLA3* 148M risk allele have the highest risk for

developing and experiencing progression and poor outcomes, including NASH cirrhosis, HCC and mortality as compared to non-carriers of the risk allele (Grimaudo et al 2020, Salameh et al 2016, Unalp-Arida and Ruhl 2020, Walker et al 2020, Wijarnpreecha et al 2021, Xu et al 2015). Additionally, an increased risk of poor outcome and all-cause mortality is present in participants homozygous for *PNPLA3* 148M as compared with heterozygous carriers and non-carriers (Unalp-Arida and Ruhl 2020).

2.3.3 Overall Benefit: Risk Conclusion

Participants taking part in this study will not necessarily benefit from administration of AZD2693. In contrast, participants may experience AEs related to study intervention or procedural complications, eg, nausea or light-headedness following blood draws, slight skin irritation from the adhesive on the ECG electrodes, or liver biopsy complications. At present, AZD2693 is being tested in humans; final data from the SAD study (D7830C00001) and preliminary data from the MAD studies (D7830C00002 and D7830C00006) have been analysed to determine the dose levels for this study, as described in Section 4.1.

Non-clinical and emerging clinical data support the administration of AZD2693 according to the proposed study design. Using the inclusion and exclusion criteria, individual stopping criteria, risk mitigation, iSMC and safety monitoring described in the CSP to avoid exposing the participants participating in studies to unacceptable risks, it is concluded that the potential benefits of evaluating AZD2693 as a potential treatment for NASH outweigh the risks.

3 OBJECTIVES, ENDPOINTS AND ESTIMANDS

The objectives and endpoints for the study are provided in Table 2.

Table 2 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the effect of AZD2693 versus placebo on histological resolution of NASH in participants with non-cirrhotic NASH with fibrosis (and homozygous for the *PNPLA3* rs738409 148M risk allele)	• Proportion of participants achieving NASH resolution [a] without worsening of fibrosis [b] based on histology after Week 52
Secondary	
• To assess the effects of AZD2693 versus placebo on histological fibrosis improvement	• Proportion of participants with at least one stage of liver fibrosis improvement with no worsening of NASH [c] based on biopsy after Week 52
• To assess the effect of AZD2693 versus placebo on ≥ 2-point improvement in NAS	• Proportion of participants with ≥ 2-point improvement from baseline in NAS based on biopsy after Week 52
• To assess the effect of AZD2693 versus placebo on improvement in fibrosis by at least one	• Proportion of participants with improvement in fibrosis by at least one stage based on biopsy after Week 52
Safety	
• To assess safety and tolerability of AZD2693 compared with placebo in participants with non-cirrhotic NASH with fibrosis	• Safety and tolerability will be evaluated in terms of AEs, vital signs, ECG, and clinical and laboratory evaluation including platelet count
Tertiary/Exploratory [d]	
• To assess the effect of AZD2693 versus placebo on resolution of NASH and improvement in fibrosis	• Proportion of participants with both resolution of NASH and improvement in fibrosis by at least one stage based on biopsy after Week 52
• To assess the effects of AZD2693 versus placebo on NASH-related histological parameters	• Change from baseline to post-Week 52 in: ° NAS (0-8) ° Stage of fibrosis according to the Kleiner fibrosis classification (0-4) ° Activity component of SAF score (0-4)
• To assess the effect of AZD2693 versus placebo on circulating markers of hepatic injury and apoptosis or necrosis	• Change from baseline to post-Week 52: ° Liver enzymes (ALT, AST, GGT) ° CK-18 (M65 and M30)

Table 2 Objectives and Endpoints

Objectives	Endpoints
• To assess the effect of AZD2693 versus placebo on circulating biomarkers of fibrosis and fibrogenesis	• Change from baseline to post-Week 52: ° Collagen turnover (eg, PRO-C3) ° ELF score ° FIB-4
• To assess the effect of AZD2693 versus placebo on lipids parameters	• Change from baseline to post-Week 52: ° Total cholesterol ° LDLc ° HDLc ° Triglycerides ° FFA ° ApoB
• To explore the effect of AZD2693 on different non-invasive algorithms developed as marker of NAFLD or NASH disease activity	• Change from baseline to post-Week 52: ° NIS4 ° APRI ° NFS
• To explore the effect of AZD2693 on biomarkers for NASH comorbidities	• Change from baseline to post-Week 52: Diabetes/metabolic syndrome: ° HbA1c ° Insulin ° c-Peptide ° Plasma glucose ° HOMA-IR Renal: ° eGFR
• To explore assessment of target engagement of AZD2693	• Change from baseline to post-Week 52 in *PNPLA3* protein
• To evaluate pharmacokinetics of AZD2693	• Observed plasma concentrations of AZD2693 full-length ASOs • Population PK parameters to be reported separately
• To evaluate the immunogenicity of AZD2693	• Incidents of development of ADA and ADA titre (if participants are ADA-positive) during treatment and follow-up
• To evaluate the effect of AZD2693 on patient-reported outcomes versus placebo	• Changes from baseline to post-Week 52 in: ° NASH-CHECK ° SF-36 ° PGIS

Table 2 Objectives and Endpoints

Objectives	Endpoints
• To explore additional NASH-or *PNPLA3*-related biomarkers using remaining biopsy samples and collected histology images (including artificial intelligence-based assessments)	• Exploratory biomarker analysis that may include baseline assessments and changes from baseline. Will not be part of the CSR.
• To explore how genetic variations may affect clinical parameters, risk and prognosis of diseases and the response to medication	• Exploratory endpoints are related to the data generated from the genetic analysis of part or all of the participants' genetic information
• Not mandatory at all sites: To explore liver stiffness and liver steatosis using imaging analysis	• In a subset of participants at clinical sites with MRI-PDFF/MRE capability: ° MRE will be used to assess liver stiffness at Visits 2, 14, and 22. ° MRI-PDFF will be used to assess HFF, volume corrected HFF, and liver fat volume at Visits 2, 14, and 22.
• To explore AZD2693 treatment effects on plasma derived cell free DNA	Results will not be reported in the CSR.
• Optional: To collect and store plasma and serum samples for future research aiming to identify/explore biomarkers and mechanisms that may affect PK, PD, safety, and tolerability related to AZD2693 treatment, as well as biomarkers and mechanisms related to NASH and other cardio-renal-metabolic diseases	Results will not be reported in the CSR.
• Optional: To collect and store blood sample for future exploratory genetic research. Note: This optional sample is taken from consented participants; see Appendix D	Results will not be reported in the CSR.

[a] Resolution of NASH as defined by the NASH CRN as "any grade of steatosis, no ballooning, and only minimal (grade 1) lobular inflammation"

[b] Worsening defined by an increase of at least one stage of the Kleiner fibrosis classification

[c] Worsening defined as an increase of at least one stage of either lobular inflammation or hepatocyte ballooning or steatosis according to NASH CRN criteria

[d] Exploratory objective results may not form part of the clinical study report for this study.

ADA, anti-drug antibody; AE, adverse event; ALT, alanine aminotransferase; ApoB, Apolipoprotein B; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; CK-18, cytokeratin-18; CRN, Clinical Research Network; DNA, deoxyribonucleic acid; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ELF, enhanced liver fibrosis; FFA, free fatty acid; FIB-4, Fibrosis-4; GGT, gamma-glutamyl transferase; HbA1c, haemoglobin A1c; HDLc, high density lipoprotein cholesterol; HFF, hepatic fat fraction; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; IHC, immunohistochemistry; LDLc, low density lipoprotein cholesterol; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging – based proton density fat fraction; NAS, Non-alcoholic fatty liver disease Activity Score; NASH, non-alcoholic steatohepatitis; NASH-CHECK, Patient-Reported Outcome Measure for Non-Alcoholic Steatohepatitis; NFS, NAFLD fibrosis score; PD, pharmacodynamics; PGIS, Patient-Reported Outcome Measure for Patient Global Impression of Severity; PK, pharmacokinetic; SAF, steatosis-activity-fibrosis; SF-36, Patient-Reported Outcome Measure for General Health Status.

Primary Estimand

The primary clinical question of interest is to, in participants with non-cirrhotic NASH with fibrosis (and homozygous for the PNPLA3 rs738409 148M risk allele), assess the difference between AZD2693 and placebo in proportion achieving resolution of NASH without worsening of liver fibrosis after Week 52 (without a liver outcome) regardless of treatment discontinuation, deviations from the protocol titration schedule, changes in background medication, or use of prohibited medication or other protocol deviations.

The primary estimand is described by the following attributes:

Population: Participants will be analysed according to their randomised study intervention assignment, irrespective of the treatment they actually received. The FAS will include all randomised and treated participants who received at least one dose of study intervention irrespective of their protocol adherence, addition or modification of background medications, discontinuation of study intervention or switches to alternative medications, and continued participation in the study.

Primary endpoint: Resolution of NASH without worsening of liver fibrosis at Week 52

Treatment condition: Participants will be dosed with 25 mg or 50 mg AZD2693 or matching placebo. Permitted concomitant medications are described in Section 6.5, and restricted or prohibited concomitant medications are described in Section 6.5.1.

Intercurrent event strategies:

- **Treatment Policy Strategy:** If a biopsy is obtained within the analysis window and is not preceded by a liver outcome, the endpoint will be defined based on the observed biopsy result regardless of the occurrence of intercurrent events of treatment discontinuation, deviations from the protocol dosing schedule, changes in background medication, or use of prohibited medications or other protocol deviations.
- **Composite Strategy:** Patients experiencing liver outcome events (adjudication events of hepatic decompensation, clinical cirrhosis, DILI, hepatocellular carcinoma, and death [further defined in the CEA charter]) before the Week 52 indicate a worsening rather than an improvement in the participant's condition. Consequently, any result after a liver outcome event is considered to be a non-response or treatment failure regardless of the actual biopsy result, if available, at the endpoint. Specifically, under the composite strategy, all events occurring from randomisation to Week 52 or prior to the post randomisation biopsy will be used to define the analysis variables (further details in the SAP).

Missing data strategy: Participants with missing final histology data will be assumed to be non-responders.

Population-level summary: Difference in proportion of responders

Rationale for estimand: The endpoint and intercurrent event strategies for the primary estimand is aligned to current regulatory guidance for investigation of non-cirrhotic NASH therapies.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2b, 52-week randomised, double-blind, placebo-controlled, multi-centre, multinational trial comparing once monthly SC administration of AZD2693 in participants with non-cirrhotic NASH (F2-F3) carrying the *PNPLA3* rs738409 148M risk allele. Genotyping will be carried out by an AstraZeneca-appointed laboratory. Eligibility for the study and genotype will be reported to the investigating physician, but the genotype will not be returned to the participant. Genotyping must be completed prior to other assessments.

This Phase 2b study is planned to evaluate 2 different doses (25 and 50 mg) with corresponding injection volumes of placebo.

The study will randomise approximately 180 participants. The randomisation ratio of homozygous participants receiving AZD2693 or placebo will be 2:1.

4.2 Scientific Rationale for Study Design

The primary objective is to assess the effect of AZD2693 versus placebo on histological resolution of NASH after 52 weeks in participants with non-cirrhotic NASH with fibrosis who are homozygous for the *PNPLA3* rs738409 148M risk allele.

Patient population includes males and females, ≥ 18 years, with biopsy-proven non-cirrhotic NASH with fibrosis stages F2 or F3 who are carriers of the *PNPLA3* rs738409 148M risk allele. The primary target population for the study are participants with NASH who are homozygous for the *PNPLA3* 148M risk allele (2 copies of the PNPLA3 148M mutation); evidence shows this group has the highest risk for developing and experiencing progression and poor outcomes, including NASH cirrhosis, HCC and mortality as compared with non-carriers of the risk allele (Grimaudo et al 2020, Salameh et al 2016, Unalp-Arida and Ruhl 2020, Walker et al 2020, Wijarnpreecha et al 2021, Xu et al 2015). Additionally, an increased risk of poor outcome and all-cause mortality is present in participants homozygous for *PNPLA3* 148M as compared with heterozygous risk allele carriers and non-carriers (Unalp-Arida and Ruhl 2020).

4.2.1 Participant Input into Design

Study coordinator and patient panel interviews were conducted during the development of the study design. Previous feedback on other AZ NASH studies was also reviewed. To reduce participant burden, optional home nursing may be implemented if requested by study participants. NASH educational materials and information about what is known regarding PNPLA3 genotype risk in the population were developed to improve awareness and provide reassurance to participants about study procedures. Participant reimbursement and retention supplies were implemented to support, thank, and make the participants feel included.

4.3 Justification for Dose

This Phase 2b study is planned to evaluate 2 different doses (25 and 50 mg) with corresponding injection volumes of placebo.

The GMAD study evaluated AZD2693 doses based on predicted PNPLA3 mRNA knockdown levels (88%, 93% and 95% for AZD2693 25 mg, 50 mg and 80 mg respectively) using dose-response on PNPLA3 mRNA knockdown in human PNPLA3 transgenic mice.

The Phase 2b dose selection is supported by the observed interim results of AZD2693 on LFC assessed by MRI-PDFF following 3 monthly doses of 25 mg and 50 mg of AZD2693 in homozygous study participants in the GMAD study and totality of safety data generated in all Phase 1 studies.

Inhibition of PNPLA3 protein by PNPLA3 mRNA knockdown is expected to have effects beyond LFC reduction on inflammation and fibrosis and ultimately NASH resolution and fibrosis improvement based on human genetic validation data. The doses carried forward into Phase 2b balance selecting the doses with potential for efficacy benefits on histology-based NASH endpoints, whilst avoiding unnecessary exposure of the study population to doses that are least likely to add significant additional efficacy or doses with a potentially increased risk for safety findings in the NASH study population. These data together support conducting the Phase 2b study at two dose levels of 25 mg and 50 mg monthly.

Special Population Considerations

In the Phase 1 SAD and MAD studies, AZD2693 plasma exposure (Cmax and AUC) appeared to be higher in Asian participants compared to non-Asian participants but no apparent differences were observed in terminal phase trough plasma concentrations which are a reflection of exposure in and re-distribution of unconjugated and/or partly conjugated ASO from liver. Being a GalNAc-conjugated, hepatocyte-targeted ASO, the efficacy of AZD2693 is expected to be driven by exposure in the liver. Therefore, the same doses of AZD2693 will be used in Asian and Global participants to investigate safety and efficacy of AZD2693 for histology-based NASH endpoints in this Phase 2b study.

The completed SAD and ongoing MAD studies included healthy volunteers with normal renal function and participants with NASH with eGFR ≥ 60 mL/min/1.73 m^2. Based on urinary excretion data in healthy volunteers in the SAD study, the fraction of AZD2693 dose that was eliminated unchanged in urine was negligible. In this Phase 2b study, the inclusion criterion for renal function is further widened to include participants with moderate renal impairment with eGFR ≥ 40 mL/min/1.73 m^2. The potential impact of renal impairment on the PK of AZD2693 will be investigated utilising population PK model-based analysis of PK data collected from participants with NASH during the clinical development programme. No significant renal alterations were observed in AZD2693 GLP toxicology studies. Based on the available data in the AZD2693 clinical study programme using traditional measures, as well as a safety composite biomarker panel to aid in the detection of kidney tubular injury in Phase 1 trials in healthy volunteers (Foundation for the National Institutes of Health 2019), there is no indication of acute renal impairment/renal toxicity with AZD2693.

Other than history/presence of hepatic disease (except for hepatic steatosis, NASH) or evidence of other known forms of chronic liver disease no exclusion criteria regarding various degrees of hepatic impairment are applied in this study. In addition, predefined upper limits of liver enzymes are used as exclusion criteria. AZD2693 is not subject to metabolism by CYP P450 enzymes or hepatic transporters mediated uptake/elimination. Therefore, its systemic exposure is not expected to be altered due to reduced CYP P450 enzymes or transporter mediated elimination. A dedicated hepatic impairment study in participants with mild, moderate, and severe hepatic impairment is planned to be completed prior to initiation of Phase 3.

4.4 End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA (Section 1.3) for the last participant in the study globally.

For the purpose of Clinical Trial Transparency, the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol related activity.

United States Food and Drug Administration (FDA) requirements defines 2 completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with

different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if they have completed all phases of the study including the last visit or the last scheduled procedure shown in the SoA.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment 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 the following criteria apply:

Age

1 Participant must be 18 to 75 years of age (inclusive) at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2 Participants who consent to give blood and buccal swab samples for genetic testing and diagnostic test development for PNPLA3 rs738409 148M who are homozygous carriers (G / G genotype) for the PNPLA3 rs738409 148M risk allele, (specifically the PNPLA3 substitution rs738409 (NG 008631.1:g.10109C > G, NM 025225.3:c.444C > G, NP 079501.2:p.I148M), further referenced as PNPLA3 I148M risk allele), The genotyping samples must be provided during Visit 1, unless already obtained during the "Screening Study in Participants at risk for or with confirmed NASH."

3 Participants who accept to have one liver biopsy performed during the screening period (if no biopsy within 6 months before randomisation is available) and one at 54 weeks (Visit 22). Participants who have had a liver biopsy more than 3 months before randomisation should have stable weight (< 5% difference) within 6 months prior to screening (Visit 2).

4 Participants with histological evidence of NASH based on central pathologist evaluation of a liver biopsy obtained up to 6 months before randomisation, or during screening, fulfilling both criteria based on central pathologist evaluation:

(a) Definitive NASH with NAS ≥ 4 with ≥ 1 in each component (ie, steatosis, lobular inflammation, and ballooning).

(a) Presence of fibrosis stage F2 or F3 according to the NASH CRN fibrosis staging system.

5 If participants (with or without diabetes) are on GLP1 RA, SGLT2i or pioglitazone, the medication must be stable (no change in dose) for 6 months before screening visit (Visit 2).

6 For participants with T2DM, HbA1c ≤ 9.5% (inclusive) at screening visit, and is considered clinically stable disease (stable doses of antidiabetic medication) for 3 months prior to screening visit (Visit 2).

7 No evidence of COVID-19 signs or symptoms (fever, cough, sore throat or other symptoms) and if applicable, testing to be performed according to site-specific and local guidance.

Sex

8 Male or female

Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

(a) Male participants:

- Contraception is not required.

(b) Female participants of non-childbearing potential:

- Contraception is not required.
- Women not of childbearing potential are defined as women who are either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomisation without an alternative medical cause. The following age-specific requirements apply:
  - Women < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and follicle-stimulating hormone levels in the postmenopausal range.
  - Women ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.

(c) Female participants of childbearing potential:

- Women of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly (see below). Women of childbearing potential who are sexually active with a non-sterilised male partner must agree to use one highly effective method of birth control, as defined below, from enrolment throughout the study and until at least 12 weeks after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only and lactational amenorrhoea method are not acceptable methods of contraception. Female condom and male condom should not be used together. In all women of childbearing potential, a urine pregnancy test should be performed at any time during the trial (in addition to scheduled testing) if a menstrual period is missed, or as required by local law. A urine pregnancy test will be performed after the serum pregnancy test at screening and must be negative. In addition, a serum pregnancy test must be administered by the end of the exposure period (at the follow-up appointment).
- Highly effective birth control methods include: total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with study treatments) [(periodic abstinence eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to IP, and withdrawal are not acceptable methods of contraception], a vasectomised partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive associated with inhibition of ovulation, and Evra Patch™, Xulane™, or NuvaRing®. Women of childbearing potential must agree to use one highly effective methods of birth control, as defined above, from enrolment throughout the study and until 12 weeks after last dose of study intervention.

Informed Consent

9 Capable of giving signed informed consent as described in Appendix A, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

10 Participants who consent only to the main study may fully participate in the main study without participating in the optional component. However, to participate in the optional component of the study, the participant must:

(a) Provide signed and dated, written informed consent prior to collection of samples for future biomarker research.

(b) Provide signed and dated, written informed consent prior to collection of samples for genetic research (Optional Genomics Initiative, see Appendix D).

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1 Any clinically significant illness, medical/surgical procedure, or significant trauma within 4 weeks of the first administration of study intervention (Visit 3).

2 History of liver transplant or current placement on a liver transplant list.

3 Liver disease of other aetiologies (eg, alcoholic steatohepatitis; drug-induced, viral or autoimmune hepatitis; primary biliary cirrhosis; primary sclerosing cholangitis; hemochromatosis; alpha-1 antitrypsin deficiency; Wilson's disease) including positive results for HBsAg or hepatitis C antibody and has not received curative treatment within the last 3 years. HCV RNA PCR reflex test to be performed in participants with a positive Hepatitis C antibody titre at screening.

4 History of cirrhosis and/or hepatic decompensation, including ascites, hepatic encephalopathy, or variceal bleeding.

5 Historical persistent or pre-existing renal disease marked by eGFR < 40 mL/min/1.73 m^2 (as defined by Kidney Disease Improving Global Outcomes guidelines).

6 CV event of acute myocardial infarction/coronary artery bypass graft surgery/percutaneous coronary intervention, unstable angina, or stroke in the period 6 months before the screening visit.

7 High-degree AV block II-III, clinically significant sinus node dysfunction not treated with pacemaker and heart rate of ≤ 45 beats per minute on screening ECG (Visit 2).

8 Ventricular or atrial arrhythmias requiring treatment. Participants with permanent atrial fibrillation and optimally regulated ventricular rate who are not on medication with an anticoagulant are eligible.

9 Severe congestive heart failure (New York Heart Association Class IV).

10 History of malignancy within the last 5 years, excluding successful treatment of basal cell skin carcinoma or in situ carcinoma of cervix.

11 History of > 5% weight loss or weight gain in the 6 months prior to screening visit, plans to initiate a weight loss diet or plans to undergo bariatric surgery.

12 Recent (within 3 months of screening visit) use of drugs approved for weight loss (eg, orlistat, bupropion/naltrexone, phentermine, lorcaserin).

13 Participation in any clinical trial or use of drugs under investigation for treatment of NASH (within 6 months of screening visit) (see Section 6.5.1 for details).

14 Recent (within 6 months of screening visit) use of drugs associated with development of NAFLD (see Section 6.5.1 for details).

15 Blood dyscrasias with increased risk of bleeding including idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, or symptoms of increased risk of bleeding (frequent bleeding gums or nosebleeds).

16 History of major bleeding or high-risk of bleeding diathesis.

17 Previous bone marrow transplant.

18 History of type I diabetes.

19 Participants with a significant COVID-19 illness within 6 months of enrolment:

- Participant's diagnosis of COVID-19 pneumonia based on radiological assessment.
- Participants with diagnosis of COVID-19 with significant findings from pulmonary imaging tests.
- Participants with a diagnosis of COVID-19 requiring hospitalisation and/or oxygen supplementation therapy.

Prior/Concomitant Therapy

20 High dose vitamin E (> 400 IU), unless on a stable dose for at least 6 months prior to the baseline biopsy and not initiated after the biopsy was taken.

21 Use of anabolic steroids and systemic treatment with glucocorticosteroids for more than 7 days within 3 months prior to the screening visit.

22 Non-leucocyte depleted whole blood transfusion within 120 days of the date of the genetic sample collection (Visit 1).

23 Use of warfarin, direct and indirect thrombin inhibitors, factor Xa inhibitors or any antiplatelet therapy other than low-dose aspirin (≤ 100 mg/day); for details see Table 5.

Other Exclusions

24 Any confirmed clinically significant abnormalities in clinical chemistry, virology (including HIV), haematology or urinalysis results as judged by the investigator at the screening visit[a].

25 Confirmed platelet count < LLN at the screening visit[a].

26 Any of the following confirmed at the screening visit[a]:

(a) ALT > 5.0 × ULN

(b) TBL > 1.5 mg/dL (TBL > 1.5 mg/dL is allowed if conjugated bilirubin is < 1.5 × ULN)

(c) INR > 1.3

(d) ALP > 1.5 × ULN (unless the ALP elevation is from a non-hepatic origin as determined by a bone-specific ALP)

27 A difference in baseline serum ALT of > 50% based on 2 repeat measurements whilst establishing baseline ALT levels (a third sample could be obtained, refer to Section 8.2.5.1).

28 Any abnormal vital signs after 10 minutes supine rest, as defined in the list below, at the screening visit and/or Day −1. Out-of-range tests may be repeated once for each visit at the discretion of the investigator; participants with BP above the values defined in the list below may be rescreened after treatment has been established for hypertension.

(a) Systolic BP < 95 mmHg or > 160 mmHg*

(b) Diastolic BP < 50 mmHg or > 90 mmHg

*BP medication should be optimised according to national guidelines and per investigator judgement.

29 Any clinically significant abnormalities in rhythm, conduction or morphology of the resting ECG and any clinically significant abnormalities in the 12-lead ECG, as considered by the investigator at the screening visit and/or on Day −1. Out-of-range test may be repeated once at the discretion of the investigator.

(a) Prolonged QT interval corrected for HR using Fridericia's formula (QTcF) > 470 ms.

(b) Family history of long QT syndrome.

(c) PR (PQ) interval prolongation (> 220 ms), intermittent second- or third-degree AV block (regardless of Wenckebach block), or AV dissociation.

(d) Persistent or intermittent complete bundle branch block.

30 Known or suspected history of drug abuse (up to 2 years prior to the screening visit), as judged by the investigator; see SoA in Section 1.3 for details.

31 Positive screen for drugs of abuse at the screening visit; see SoA in Section 1.3 for details.

32 History or suspected excessive alcohol consumption defined as an average weekly intake of > 21 drinks/week for males or > 14 drinks/week for females. One drink is equivalent to 14 g alcohol. The participant should not have alcohol dependence (assessed by Alcohol Use Disorders Identification Test questionnaire, with a score of ≥13 for women and ≥15 for men indicating alcohol dependence, see Appendix K).

33 History of severe allergy/hypersensitivity or ongoing clinically significant allergy/hypersensitivity, as judged by the investigator or history of hypersensitivity to drugs with a similar chemical structure or class to AZD2693.

34 Plasma donation within 1 month of the screening visit or any blood donation/blood loss > 500 mL during the 3 months prior to the screening visit.

35 Vulnerable participants, eg, kept in detention, protected adults under guardianship, trusteeship or committed to an institution by governmental or juridical order.

36 Involvement of any AstraZeneca study site employee or their close relatives.

37 Judgement by the investigator that the participant should not participate in the study if they have any ongoing or recent (ie, during the screening period) minor medical complaints that may interfere with the interpretation of study data or are considered unlikely to comply with study procedures, restrictions, and requirements.

38 Participants who cannot communicate reliably with the investigator or designee.

39 For women only - currently pregnant (confirmed with positive pregnancy test) or breast-feeding.

a Confirmed is defined as at least one repeated measure within one week.

5.3 Lifestyle Considerations

1 Participants should be counselled to follow standard lifestyle management set forth for participants with NAFLD/NASH and or T2DM per local guidance, and if available at the site, a consultation with a nutritionist. Once counselled, they will be advised to adhere to dietary and lifestyle recommendations from screening until the end of the safety follow-up period and will be reminded at each study visit.

2 Participants who are blood donors should not donate blood for the duration of the study and for 3 months following their last follow-up visit.

5.3.1 Meals and Dietary Restrictions

Participants should fast for at least 8 hours, ie, no food or beverage except water, prior to each visit with laboratory component except for specific visits (V1, V6, V8, V10) as per SoA. Prior to MRI-PDFF/MRE assessments, at least 4 hours of fasting in the morning is required. For more details, see the SoA (Section 1.3).

5.3.2 Alcohol

Participants with known or suspected history of alcohol abuse, as judged by the investigator, are not allowed to participate in the study. Refer to exclusion criteria 32 (see Section 5.2) and see Appendix K.

5.3.3 Activity

Participants should refrain from intense exercise for 24 hours prior to each visit.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. 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 (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, medical history, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Only one-time rescreening is allowed in the study if the reason for screen failure was transient (including, but not limited to, study-supplied equipment failure, positive test results for COVID-19, study assessment failure and sample analysis delays [up to 7 days delayed] or unforeseen personal events that mandate missed screening visits). Participants are allowed one set of rescreening for laboratory results or one retest of a specific test if a clinically transient condition has likely contributed to previous out-of-range results, with the exception of ALT, in which no rescreening, apart from the initial baseline measurements (up to 3), is allowed (See Section 8.2.5.1). Rescreened participants should be assigned the same participant number as for the initial screening.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 90 days of the previous ICF signature date. If a historical biopsy is being used for a participant undergoing rescreening, study staff must ensure that the historical biopsy is still eligible (ie, within 6 months of randomisation).

Individuals who are not carriers of the *PNPLA3* rs738409 148M risk allele are prohibited from rescreening.

Once a participant has a genotype result confirmed from the central lab for *PNPLA3* I148M and is determined to be a risk allele carrier, no further genotype testing is required if the participant is rescreened.

Participants that after rescreening are still deemed to be screen failures will have the option, if they wish, to be contacted in the future for an observational study aimed to gain further insights into the natural progression of the disease.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered or medical device(s) utilised by a study participant according to the study protocol.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

The investigational products to be used during the study are detailed in Table 3.

Table 3 Investigational Products

Intervention name	AZD2693	Placebo
Type	Drug	Drug
Dose formulation	Solution for SC injection	Solution for SC injection
Unit dose strength(s)	25 mg/mL and 80 mg/mL	Sodium chloride 0.9% solution
Dosage level(s)	25 mg and 50 mg once per month [a]	Saline solution (to match volume of AZD2693 injection volume) once per month
Route of administration	SC injection [b]	SC injection [b]
Special handling requirements	Separate handling instructions will be provided.	Separate handling instructions will be provided.
Specific device for drug administration	Specifications for syringes and needles for injection will be provided by AstraZeneca	Specifications for syringes and needles for injection will be provided by AstraZeneca
Use	Experimental	Placebo
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by AstraZeneca	Provided centrally by AstraZeneca
Packaging and labelling	Study Intervention will be provided as labelled vials packaged in labelled cartons. Labels will be prepared in accordance with GMP and local regulatory guidelines.	Study Intervention will be provided as labelled vials packaged in labelled cartons. Labels will be prepared in accordance with GMP and local regulatory guidelines.

[a] Dosage level will be prepared using available unit strengths. For details on preparation, see the handling instructions.

[b] Subcutaneous injection should be rotated between three injection sites; the abdomen (avoiding a 5 cm radius around umbilicus), upper arm and thigh. The anatomical location of each injection site should be documented in the eCRF. Subcutaneous injection should be administered using a skin pinch and insertion of the needle at a 45° angle. Subcutaneous injection should be administered using gentle pressure over at least 5 seconds, holding the needle in place for a further 5 seconds before withdrawing the needle. Participants are also recommended to refrain from intense activity and exposure to extreme temperature changes for 3 hours following injection.

GMP, good manufacturing practice; IMP, investigational medicinal product; SC, subcutaneous.

AZD2693 and placebo will be supplied as solutions for injection. AZD2693 25 mg and 50 mg will be supplied in a vial containing 25 mg/mL AZD2693 and 80 mg/mL AZD2693 respectively.

6.2 Preparation/Handling/Storage/Accountability

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

2 Only participants enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff. The intervention handling instructions will be provided in a separate Handling Instructions document.

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

4 Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual. Participants will receive a leaflet or card that provides address, telephone number and the main contact for information on the study intervention and clinical study.

6.2.1 Dose preparation

The dose of AZD2693 and placebo for administration must be prepared by trained personnel using standard aseptic techniques and documented according to local procedures. Dose preparation should occur in a validated aseptic suite where available.

If prepared in a validated aseptic suite, the syringes can be held for no more than 24 hours at refrigeration (2°C to 8°C), out of which up to 4 hours may be at room temperature (below 25°C), from the time of needle puncture, administration time included. After this time, any unused solution must be discarded. If the syringes are stored, place a new needle immediately before administration. If the syringes have been refrigerated, allow solution to equilibrate at room temperature for approx. 15 minutes prior to use.

If it is not possible to use a validated aseptic suite, aseptic technique (including sterile gloves and appropriate gowning) for syringe preparation must be followed and the product must be administrated within 1 hour following start of preparation. Unless administered immediately or within 1 hour, the IMP shall promptly and safely be discarded and shall not be stored for later use.

Further details for in-use storage can be found in the Handling Instructions under section "Handling and in-use stability".

The concentration and volume of AZD2693 solution for injection to be prepared, can be found in Handling instructions.

Refer to the Handling instructions and Pharmacy Manual for detailed information on dose preparation and handling procedures for AZD2693 and placebo.

6.2.2 Dose Administration

AZD2693 and placebo must reach room temperature prior to administration. Further details can be found in handling instructions.

Doses of 25 mg or 50 mg or placebo will be administered as sc injection (refer to handling instructions for the volumes to be administered for each cohort) using 27 G, 0.5" needle (or similar), according to standard procedures for [sc] injections. Subcutaneous injection should be rotated between three injection sites; the abdomen (avoiding a 5 cm radius around umbilicus), upper arm and thigh. The anatomical location of each injection site should be documented in the eCRF. Subcutaneous injection should be administered using a skin pinch and insertion of the needle at a 45° angle. Subcutaneous injection should be administered using gentle pressure over at least 5 seconds, holding the needle in place for a further 5 seconds before withdrawing the needle. Participants are also recommended to refrain from intense activity and exposure to extreme temperature changes for 3 hours following injection.

6.3 Measures to Minimise Bias: Randomisation and Blinding

All participants will be centrally assigned to randomised study intervention using an IRT/RTSM. Before the study is initiated, login information and directions for the RTSM will be provided to each site.

Study intervention will be dispensed at specific study visits as indicated in SoA (Section 1.3).

The IRT/RTSM will provide to the investigator(s) or pharmacists the kit identification number to be allocated to the participant at the dispensing visit.

Routines for this will be described in the IRT/RTSM user manual provided to each centre.

At randomisation, participants will be stratified by the presence/absence of T2DM and by fibrosis stage F2/F3. The randomisation code should not be broken except in medical emergencies when the appropriate clinical management of the participant requires knowledge of the treatment randomisation. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected, suspected to be causally related to an IP and potentially require expedited reporting to regulatory authorities.

Randomisation codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual.

6.4 Study Intervention Compliance

Participants are dosed only at the site; they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

A record of the number of AZD2693 or placebo injections administered to each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded in the eCRF.

6.5 Concomitant Therapy

Participants should be on stable medication before screening visit as discussed in Section 5, with no planned medication initiation or dose change during study participation.

Participants must have stable concomitant medication during the study period, with the exception of medication prescribed for occasional use. If the study intervention or participant's health necessitates a change in concomitant medication, changes can be made as judged by the investigator. If the medication is suspected to interfere with the disease being studied (NASH), it is recommended to discuss with the study physician, with the exception of emergency use medications.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the participant is receiving at the time of enrolment 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 Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Prohibited Concomitant Medications

Participants must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

Use of the following medications will be restricted (Table 4) or prohibited (Table 5) as specified:

Table 4 Restricted Medications

Medication/class of drug:	Restrictions for Usage (including limits for duration permitted and special situations in which it is allowed):
Herbal preparations or dietary supplements marketed for control of body weight or appetite	Concurrent or prior use within 1 week prior to the screening visit and during the study.
Systemic corticosteroids by oral, intravenous, intra-articular, or intramuscular route	Within 3 months prior to the screening visit and during the study unless prescribed for a very brief period of less than 7 days.
Vitamin E (high doses > 400 IU)	Concurrent use, unless on a stable dose for at least 6 months prior to historical biopsy or screening biopsy and no changes made during study.
Pioglitazone or other PPAR-γ agonists; GLP1 RA or therapies containing GLP1 RA, SGLT2i	Concurrent use, unless on a stable dose for at least 6 months prior to the screening visit and no changes made during study.

GLP1 RA, glucagon-like peptide-1 receptor agonist; IU, international units; PPAR-γ, peroxisome proliferator-activated receptor gamma.

Table 5 Prohibited Medications

Prohibited medication/class of drug:	Prohibited Usage
Therapies associated with development of NAFLD such as methotrexate, tamoxifen, amiodarone, or long-term use of tetracyclines	Within 6 months of screening visit. In the case of tetracyclines, these drugs are restricted during the study unless prescribed for a very brief period of less than 7 days.
Therapies in classes under investigation or approved during the study for the treatment of NASH (except for SGLT-2 inhibitors and PPAR-γ agonists), such as obeticholic acid and resmetirom	Within 6 months of screening visit and during the study.
Drugs approved for weight loss (eg, orlistat, bupropion/naltrexone, phentermine-topiramate, phentermine, lorcaserin), as well as those drugs used off-label	Within 3 months of screening visit and during the study.
Warfarin, direct, and indirect thrombin inhibitors, factor Xa inhibitors or any antiplatelet therapy other than low-dose aspirin (≤ 100 mg/day)	Within 1 week of screening visit and during the study.

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PPAR-γ, peroxisome proliferator-activated receptor gamma; SGLT-2, sodium-glucose co-transporter 2.

6.5.2 Permitted and Prohibited Therapies for the Management of Type 2 Diabetes Mellitus

If the participant is diagnosed with T2DM during the trial, based on a HbA1c of 6.5% or higher, or a fasting plasma glucose of 126 mg/dL or higher on 2 separate occasions, the participant should be treated with standard management, including metformin or appropriate therapy and referred to their primary care physician for further management.

6.6 Dose Modification

Dose modifications are not permitted. Treatment stopping criteria are only applied if participants develop potential DILI as described in Section 6.6.1.

6.6.1 Monitoring and Management Plan for Possible DILI

According to consensus guidelines developed through the IQ DILI Initiative within the International Consortium for Innovation and Quality in Pharmaceutical Development, Hy's Law criteria are intended for participants without underlying liver disease, presenting a significant challenge within the context of clinical trials for participants with NASH. AstraZeneca will use an algorithm for monitoring and management of possible drug-induced liver injury in Phase 2b NASH clinical trial in participants with normal and elevated baseline ALT based on the IQ DILI Initiative consensus guideline and illustrated in Table 6.

Flowcharts to reflect the algorithm are illustrated in Figure 2 and Figure 3. Stopping criteria for possible cholestatic DILI is described in Table 7.

How to determine the baseline ALT value is described in Section 8.2.5.1.

Table 6 Algorithm for Monitoring and Management of Possible Hepatocellular DILI in NASH Clinical Trials in Patients With Normal or Elevated Baseline ALT (>1.5 x ULN)[a]

Treatment Emergent ALT Elevations	TBL Values at Time of Treatment Emergent ALT Elevation	Presence of Liver-Related Symptoms [b]	Action
Normal/near normal baseline[c]: ≥ 3 x ULN but < 5 x ULN Elevated baseline[c]: ≥ 2 x baseline but	< 2 x ULN Participants with Gilbert's syndrome: direct bilirubin < 2 x baseline AND INR < 1.5	Absent	Continue dosing. Repeat ALT, AST, ALP, TBL in 2-5 days, and thereafter as clinically indicated. Follow-up for symptoms.
		Present	Continue dosing. Repeat ALT, AST, ALP, TBL in 2-3 days, and thereafter as clinically indicated. Follow-up for symptoms.

< 3 x baseline AND < 300 U/L			Initiate evaluation for other aetiologies of abnormal liver tests (incl. Hy's law kit (Appendix E 7)). If ALT or TBL is rising on repeated testing, perform liver biochemistry within 7 days prior to next scheduled dose and review results prior to dosing.
	TBL ≥ 2 x ULN or INR > 1.5 Participants with Gilbert's syndrome: direct bilirubin ≥ 2 x baseline or INR > 1.5	Irrespective of symptoms	Interrupt study intervention. Initiate close monitoring as clinically indicated. Initiate evaluation for other aetiologies of abnormal liver tests (incl. Hy's law kit (Appendix E 7)). Study intervention can be continued or restarted only if another aetiology is identified, and liver biochemistry and any liver-related symptoms return to baseline.
Normal/near normal baseline[c]: ≥ 5 x ULN but < 8 x ULN Elevated baseline[c]: ≥ 3 x baseline but < 5 x baseline AND < 500 U/L or ≥ 300 U/L AND < 500 U/L AND < 5 x baseline	< 2 x ULN Participants with Gilbert's syndrome: direct bilirubin < 2 x baseline AND INR < 1.5	Absent	Continue dosing Repeat ALT, AST, ALP, TBL in 2-3 days, and thereafter as clinically indicated. Follow-up for symptoms. Initiate evaluation for other aetiologies of abnormal liver tests (incl. Hy's law kit (Appendix E 7)). If ALT or TBL is rising on repeated testing, perform liver biochemistry within 7 days prior to next scheduled dose and review results prior to dosing. **If ALT is elevated > 2 weeks:** Normal/near normal baseline[c]: If ALT remains elevated > 5 x ULN for >2 weeks, interrupt study intervention. Elevated baseline[c]: If ALT remains elevated ≥ 3 x baseline and ≥ 300 U/L for >2 weeks, interrupt study intervention. Study intervention can be continued or restarted only if another aetiology is identified, and liver biochemistry and any liver-related symptoms return to baseline.

		Present	Interrupt study intervention. Initiate close monitoring. Initiate evaluation for other aetiologies of abnormal liver tests (incl. Hy's law kit (Appendix E 7)). Study intervention can be continued or restarted only if another aetiology is identified, and liver biochemistry and any liver-related symptoms return to baseline.
	TBL ≥ 2 x ULN Participants with Gilbert's syndrome: direct bilirubin ≥ 2 x baseline or INR > 1.5	Irrespective of symptoms	Interrupt study intervention. Initiate close monitoring. Initiate evaluation for other aetiologies of abnormal liver tests (incl. Hy's law kit (Appendix E 7)). Study intervention can be continued or restarted only if another aetiology is identified, and liver biochemistry and any liver-related symptoms return to baseline.
Normal/near normal baseline[c]: ≥ 8 x ULN Elevated baseline[c]: ≥ 5 x baseline or ≥500 U/L	Irrespective of TBL	Irrespective of symptoms	Interrupt study intervention. Initiate close monitoring. Initiate evaluation for other aetiologies of abnormal liver tests (incl. Hy's law kit (Appendix E 7)). Study intervention can be continued or restarted only if another aetiology is identified, and liver biochemistry and any liver-related symptoms return to baseline.

[a] Adapted from: (Regev et al 2019), with adjustments from the FDA DILI guideline [https://www.fda.gov/media/116737/download] and AZD2693 data.

[b] Liver-related symptoms include severe fatigue, nausea, vomiting, and right upper quadrant pain.

[c] Baseline ALT is derived from an average of 2 pre-treatment ALT measurements at least 2 weeks apart. Elevated baseline is defined as ALT ≥ 1.5 x ULN. If on treatment a participant has 2 or more consecutive ALT values, at least 2 weeks apart, each less than 50% of the baseline ALT with any 2 consecutive values being within 40% of each other (with percentage calculated based on the larger value as the denominator), then a new baseline should be set to be the minimum of the latest consecutive pair of values that are *stable* (ie, within 40% of each other). A central laboratory must be used for all ALT measurements. For more information, see Section 8.2.5.

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; DILI, drug-induced liver injury; INR, international normalised ratio; TBL, total bilirubin; ULN, upper limit of normal.

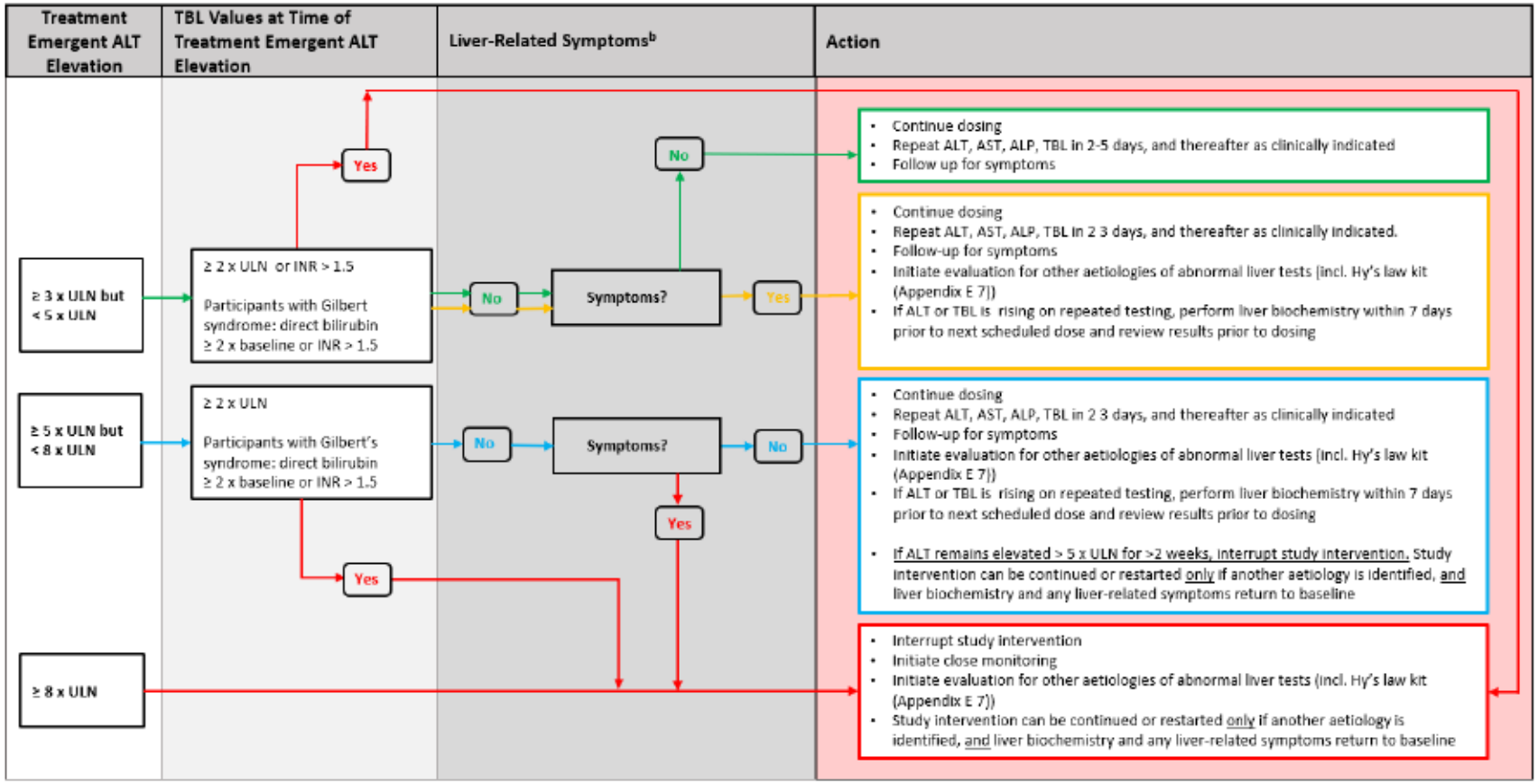
Table 7 Stopping Criteria for Possible Cholestatic DILI

Criteria	Action
• ALP ≥ 2 x ULN and DBL ≥ 2 x ULN (if participant has Gilbert's syndrome) • ALP ≥ 2 x ULN and TBL ≥ 2 x ULN (if participant does not have Gilbert's syndrome) • ALP ≥ 2 x ULN and TBL (without Gilbert's) / DBL (with Gilbert's) ≥ 2 x ULN and INR > 1.5 • ALP ≥ 2 x ULN and TBL (without Gilbert's) / DBL (with Gilbert's) ≥2 x ULN and presence of liver-related symptoms [a]	Interrupt study intervention. Initiate close monitoring and workup for competing aetiologies. Study intervention can be restarted only if another aetiology is identified, and laboratory and clinical symptoms have resolved.

[a] Liver-related symptoms include severe fatigue, nausea, vomiting, right upper quadrant pain.

ALP, alkaline phosphatase; DBL, direct bilirubin; DILI, drug-induced liver injury; INR, international normalised ratio; TBL, total bilirubin; ULN, upper limit of normal.

Figure 2 **Flowchart for Monitoring and Management of Possible Hepatocellular DILI in NASH Participants with Normal/Near Normal (< 1.5 x ULN) ALT at Baseline[a]**

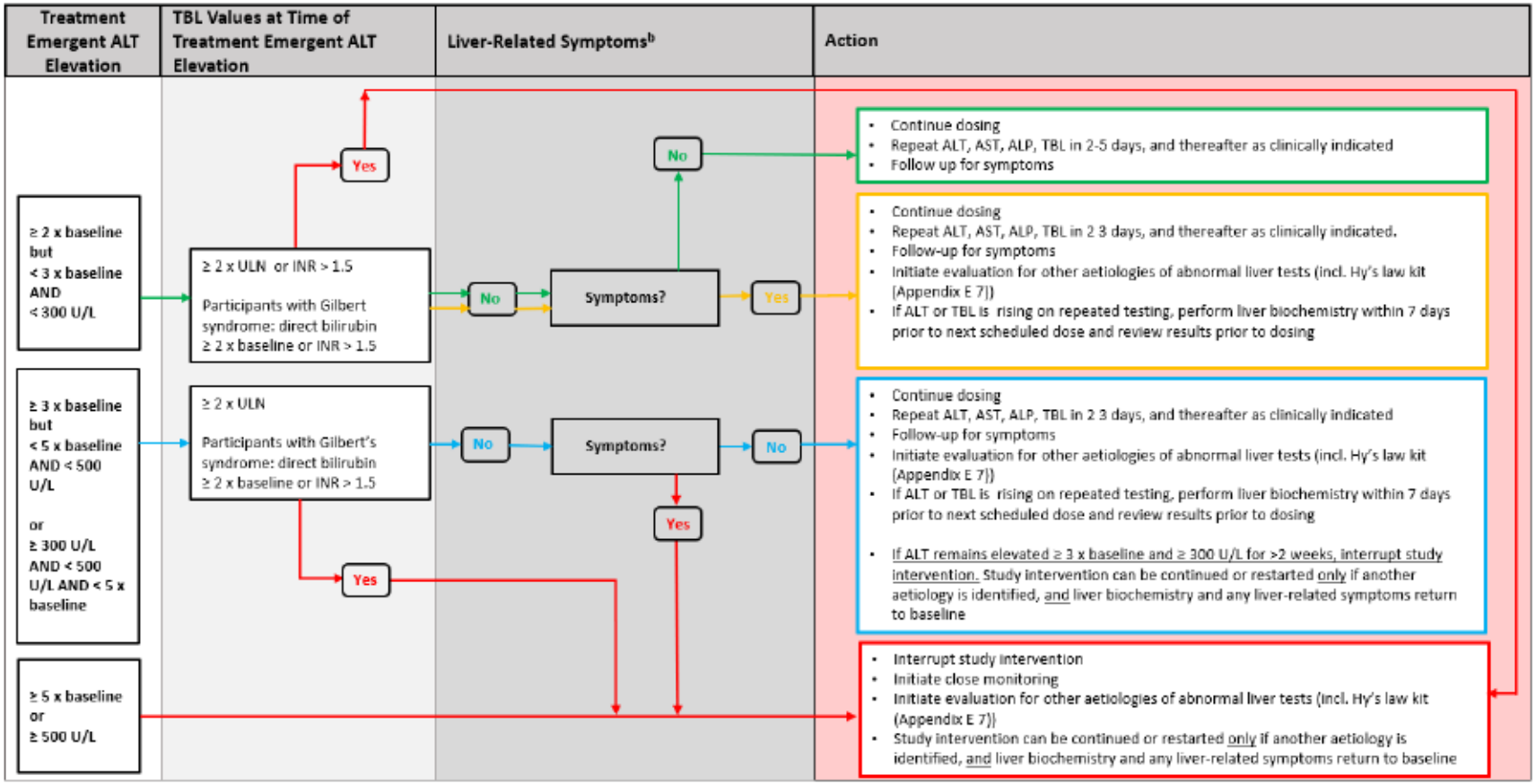


[a] Baseline ALT is derived from an average of 2 pre-treatment ALT measurements at least 2 weeks apart. Elevated baseline is defined as ALT ≥ 1.5 x ULN. If on treatment a participant has 2 or more consecutive ALT values, at least 2 weeks apart, each less than 50% of the baseline ALT with any 2 consecutive values being within 40% of each other (with percentage calculated based on the larger value as the denominator), then a new baseline should be set to be the minimum of the latest consecutive pair of values that are stable (ie, within 40% of each other). A central laboratory must be used for all ALT measurements. For more information, see Section 8.2.5.

[b] Liver related symptoms include severe fatigue, nausea, vomiting, right upper quadrant pain

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; INR, international normalised ratio; TBL, total bilirubin; ULN, upper limit of normal

Figure 3 **Flowchart for Monitoring and Management of Possible Hepatocellular DILI in NASH Participants with Elevated ALT at Baseline (>1.5 x ULN)[a]**



[a] Baseline ALT is derived from an average of 2 pre-treatment ALT measurements at least 2 weeks apart. Elevated baseline is defined as ALT ≥ 1.5 x ULN. If on treatment a participant has 2 or more consecutive ALT values, at least 2 weeks apart, each less than 50% of the baseline ALT with any 2 consecutive values being within 40% of each other (with percentage calculated based on the larger value as the denominator), then a new baseline should be set to be the minimum of the latest consecutive pair of values that are stable (ie, within 40% of each other). A central laboratory must be used for all ALT measurements. For more information, see Section 8.2.5.

[b] Liver related symptoms include severe fatigue, nausea, vomiting, right upper quadrant pain.

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; INR, international normalised ratio; TBL, total bilirubin; ULN, upper limit of n

6.7 Intervention After the End of the Study

There will be no study intervention provided after the end of the study.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

Participants may be discontinued from study intervention in the following situations (note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study):

- Participant decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment.
- AE or other safety reasons as judged by the investigator and/or sponsor where continued treatment may put the participant at undue risk.
- Severe noncompliance with the CSP.
- Pregnancy; if a participant becomes pregnant during the study the study intervention should be discontinued immediately and an AstraZeneca representative notified.
- Platelet count $< 75 \times 10^9$/L, confirmed by taking a second measurement (Appendix F)
- Signs or symptoms of severe hepatic impairment including abnormal laboratory values or possible cholestatic DILI as described in Table 6 and Table 7.
- Confirmed by repeat testing increase in serum creatinine of 0.3 mg/dL from baseline at the discretion of the investigator
- Confirmed by repeat testing 25% decline in eGFR from baseline at the discretion of the investigator
- New onset haematuria of unknown aetiology, confirmed by repeat testing, albuminuria (urine albumin/creatinine ratio [UACR] $\geq$ 300 mg/g), or proteinuria (urine protein/creatinine [UPCR] $\geq$ 500 mg/g) at the discretion of the investigator
- Anaphylactic reaction or severe hypersensitivity reaction suspected to be related to study intervention.

Participants who discontinue study treatment should not be automatically withdrawn from the study. Measures will be taken to prevent and minimise missing data and to continue to collect data, and participants should be followed up until the follow-up visit unless their consent was withdrawn from the main study. In the event that participants have completed 36 weeks treatment, they will be invited for a biopsy to assess efficacy as well as evaluate disease progression status.

Follow-up for Participants who have Permanently Discontinued Study Intervention

Eligible Participants who are prematurely and permanently discontinued from receiving the study intervention will continue their study participation by following the original visit schedule, without taking the study intervention or undergoing any study intervention-related procedures.

7.1.1 Temporary Discontinuation of Study Intervention

If a participant temporarily discontinues study intervention for any reason, the participant may restart the medication at any time during the dosing period in accordance with the dosing schedule. If temporary discontinuation is due to any safety concern, they must undergo an assessment of clinical safety labs within 14 ± 3 days (or according to specific guidance, such as for ALT and platelets) of planned administration and re-assessment of the participants clinical status. No additional doses will be administered to make up for missed doses. The reason for any temporary study intervention interruption will be collected in the eCRF.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at their own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options and encouraged to continue with one of the options provided (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an Early Study Discontinuation Visit should be conducted, as shown under EDV in the SoA (Section 1.3). See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
  - The participant will discontinue the study intervention and be withdrawn from the study at that time.
  - If a participant has completed at least 36 weeks of the intervention at the time of choosing to withdraw, they are eligible to complete an exit biopsy 2 weeks (± 7 days) after the last dose received and should be counselled on this option. Details are in the SoA (Section 1.3).
- 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, it should be confirmed if they still agree for existing samples to be used in line with the original consent. If they request withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The

investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are 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 and 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, they will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomised, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- 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. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The amount of blood collected from each participant over the duration of the study, will be approximately 960 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

8.1.1 Liver Biopsy-based Histopathology

Liver biopsy samples taken at baseline (either historical [collected within 6 months before randomisation] or taken during the screening period) and after Week 52 will be assessed centrally by a Central Pathology Review Committee to determine the NAS and fibrosis staging. Details of liver biopsy procedure are described in the Histopathology Manual. See Appendix H for a description of NAS and fibrosis stages.

Additional evaluations of histopathology images may be used to explore NASH biology and/or PNPLA3 treatment effects. This will not be part of the CSR.

8.1.2 Biomarkers

Blood samples will be collected under fasting conditions for measuring circulating biomarkers to evaluate the effect of AZD2693 on liver function (ALT, AST, GGT) and lipid metabolism (Lipid Panel), as listed in Table 9 and for other PD-specific measurements as shown in Table 8.

Table 8 Pharmacodynamic Biomarkers

PD biomarkers	
CK18 M30 and M65	β-Hydroxybutyrate
Inflammation protein biomarker panel	Collagen turnover (eg, Pro-C3)
ApoB	
ELF score	
Tissue Inhibitor of metalloproteinase 1 (TIMP1)	Hyaluronic acid (HA)
Type 3 procollagen peptide (P3NP)	
NIS-4	
miR-34a-5p	YKL-40
alpha2-macroglobulin	Hemoglobin A1c (HbA1c)

In addition, FIB-4, APRI and NFS will be calculated on available data at visits according to SoA (Section 1.3).

Cell free DNA will be extracted from plasma and effect of AZD2693 treatment on abundance, methylation pattern and sequence will be explored.

8.1.3 MRI-PDFF/MRE

In a subset of participants at selected clinical sites with the required MRI capability, MRE, MRI-PDFF and volumetric MRI will be used to assess liver stiffness, HFF and liver volume respectively. Liver fat volume will be assessed from the HFF and liver volume measurements. The assessments will be done for the time points specified in the SoA (Section 1.3). MRI-PDFF/MRE should be performed with at least 4 hours of fasting and within a ± 2-hour window from the baseline scan. The subset will include approximately 26 participants per arm who are homozygous for the *PNPLA3* 148M risk allele and are able to perform MRI-PDFF/MRE assessments. For additional details, refer to the Imaging Manual.

8.2 Safety Assessments

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

8.2.1 Physical Examinations

- A complete physical examination will include assessments of the following: general appearance, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, and respiratory, CV, and muscular-skeletal.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, CV system, and abdomen (liver and spleen).

Physical examination will be performed at timepoints as specified in the SoA (Section 1.3).

8.2.2 Height, Weight, and Waist Circumference

Standing height, body weight and waist circumference will be measured according to the schedule presented in the SoA (Section 1.3). Height will be measured once at screening and recorded in centimetres.

Body weight should be measured in the morning whilst the participant is fasted and prior to breakfast. The participant's weight should be measured with the participant wearing a surgical gown and no shoes, and the weight of the surgical gown should be subtracted from the result. If a surgical gown is not available, the weight of the participant should be obtained while the participant is wearing light clothing; this should remain consistent throughout the trial. The participant's body weight will be recorded in kilograms (kg) to 1 decimal place. All readings should be recorded as accurately as possible, and the same scale should be used for all assessments for a given participant. The same scale should be used throughout the study and calibrated on a regular basis as recommended by the manufacturer.

Waist circumference will be measured at the same time points as body weight. The correct position for measuring waist circumference is midway between the uppermost border of the iliac crest and the lower border of the costal margin. With the participant in the standing position, a non-stretchable measuring tape of adequate length should be placed around the abdomen at the level of this midway point and a reading taken when the tape is snug but does not compress the skin, and at the end of a normal respiratory expiration. Waist circumference should be measured twice and recorded in centimetres to one decimal place. If the measurements are within 1 cm of one another, the average should be calculated. If the difference between the 2 measurements exceeds 1 cm, the 2 measurements should be repeated.

8.2.3 Vital Signs

The following BP and pulse rate variables will be collected after the participant has rested in the supine position for at least 10 minutes for screening visit and in subsequent visits after resting in a sitting position for 5 minutes:

- Systolic BP (mmHg)
- Diastolic BP (mmHg)
- Pulse (bpm)

Blood pressure will be measured in triplicate, after stabilisation, with all readings measured within 5 minutes and averaged to provide the measurement to be recorded in the eCRF.

Temperature will be measured; oral, temporal, and tympanic measurements are allowed but should be consistent throughout the study. Axillary measurements are allowed but are not the preferred method for temperature assessment.

Vital signs measurements will be performed at the visits/timepoints indicated in the SoA (Section 1.3).

8.2.4 Electrocardiograms

At the visits and timepoints specified in the SoA (Section 1.3), triplicate 10-second, 12-lead safety ECG will be obtained after 10 minutes of supine rest, using the study site's own ECG machines.

ECG recordings will be performed prior to study intervention administration if applicable/scheduled. Starting from Visit 9 (Week 12), ECGs will be recorded approximately every 12 weeks; extra ECGs may be performed at the request of an investigator. ECG recording should be performed prior to any blood draw.

The PI will review each of the 3 ECG replicates for abnormality in cardiac intervals of RR, PR, QRS, QT, and QTcF and the heart rate. QTcF will be calculated by averaging the readings from 3 replicates. The 3 ECG replicates will be stored in the participant study file.

The PI will interpret the findings as normal, abnormal clinically nonsignificant, or abnormal clinically significant. This evaluation will be reported in the eCRF. Additionally, clinically significant findings should be documented on the AE page of the eCRF if applicable. The PI may add extra safety assessments using resting 12-lead ECG if needed. These assessments should be entered as unscheduled assessments.

8.2.5 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the visits indicated in the SoA (Section 1.3).

The clinical chemistry, haematology, and urinalysis will be performed at a central laboratory.

For the following visits the only clinical safety laboratory assessments that are required are as follows:

- Visit 6: platelet count and ALT monitoring
- Visit 8: platelet count and ALT monitoring
- Visit 10: platelet count, ALT monitoring and GLDH

Monitoring of ALT will be every 2 weeks for 4 months (up to and including Week 16), and monthly thereafter.

Platelet count will be monitored every 2 weeks for 4 months (up to and including Week 16), and monthly thereafter.

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. At the investigators' discretion, repeat testing can be performed at a local laboratory. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The date, time of collection and results (values, units, and reference ranges) will be recorded in participant source documents and in the appropriate eCRF.

AEs based on examination and test should be reported as described in Section 8.3.6.

The following laboratory variables as presented in Table 9 will be measured.

Table 9 Laboratory Safety Variables

Haematology (whole blood)	
• B-White blood cell (WBC) count	• B-Mean corpuscular haemoglobin concentration (MCHC)
• B-Red blood cell (RBC) count	• B-Neutrophils absolute count
• B-Platelet count	• B-Lymphocytes absolute count
• B-Haemoglobin (Hb)	• B-Monocytes absolute count
• B-Haematocrit (HCT)	• B-Eosinophils absolute count
• B-Mean corpuscular volume (MCV)	• B-Basophils absolute count
• B-Mean corpuscular haemoglobin (MCH)	• B-Reticulocytes absolute count
Clinical chemistry (serum or plasma)	
• Creatinine	• Uric acid
• Bilirubin, total and direct	• Urea
• Alkaline phosphatase (ALP)	• Phosphate
• Aspartate transaminase (AST)	• Bicarbonate
• Alanine transaminase (ALT)	• Thyroid stimulating hormone (TSH; screening)
• Gamma-glutamyl transferase (GGT)	• Glucose
• Potassium	• Insulin
• Calcium, total	• C-peptide
• Sodium	• Haemoglobin A1C (HbA1C) [a]
• Magnesium	• Glutamate dehydrogenase (GLDH) [c]
Urinalysis (dipstick)	
• Blood	• Glucose
• Protein	• Microscopy (if positive for protein or blood)
Renal safety biomarkers [b]	
• Total protein	• Creatinine
• Albumin	
Coagulation	
• International normalised ratio (INR)	• Prothrombin time (PT)
• Activated partial thrombin time (APTT)	
Additional laboratory variables	• Retinol
• Estimated glomerular filtration rate (eGFR)	• Retinol binding protein-4 (RBP-4)
Inflammatory panel	
• High-Sensitivity C-reactive protein (hs-CRP)	• Fibrinogen
• Albumin	• Monocyte chemoattractant protein-1 (MCP-1)
• Complement C3 and C5 (Total, not activated complement)	• Interleukin-6 (IL-6)
Thyroid panel	
• Free thyroxine (free T4)	• Thyroid-stimulating hormone (TSH)
Lipid Panel	

Table 9 Laboratory Safety Variables

• Low Density Lipoprotein (LDL, measured) • High Density Lipoprotein (HDL) • Free fatty acid (FFA)	• Triglycerides (TG) • Total Cholesterol
Complement Activation Panel	
• C5a	• Bb

[a] HbA1c assessments performed at screening, Day 1, and Week 12, 24, 36, 52, and 64 (or follow-up visit 12 weeks post-dose).

[b] Urine sample. UACR and UPCR will be calculated.

[c] Glutamate dehydrogenase (GLDH) assessment performed at baseline and Week 14.

In case a participant shows an ALT or AST ≥ 3 x ULN please refer to Table 6 and Appendix E (Actions required in cases of increases in liver biochemistry and evaluations of Hy's Law) for further instructions.

8.2.5.1 Establishing the Baseline ALT Value

Baseline ALT values should be established by calculating the average of 2 pre-treatment measurements (obtained at least 2 weeks and no more than 8 to 12 weeks apart), to account for disease-related changes in ALT whilst in the study that may otherwise be inappropriately attributed to the study intervention. The differences in 2 repeat measurements of baseline serum ALT should be ≤ 50% to be eligible for study entry.

If the initial variability between the 2 baseline measurements is > 50%, a third measurement should be obtained in the screening period. If the third measurement is obtained and the participant is enrolled in the study, the baseline ALT should be derived from the 2 of the 3 measurements that are ≤ 50% in variability and that are closely reflecting the true baseline value based on participant medical history, previous ALT values and investigators' judgement.

An AstraZeneca-appointed central laboratory should be used for all baseline ALT measurements (no local or historical tests permitted).

Investigators should ensure that the underlying disease is considered stable at the point of enrolment. Participants with rapidly changing ALT, based on the screening laboratory values used to establish the baseline, should delay enrolment until the underlying cause is determined or until ALT stabilises.

If, during treatment, a participant has 2 or more consecutive ALT values at least 2 weeks apart that are < 50% of the baseline ALT – each with any 2 consecutive values within 40% of each other (percentage calculated using the larger value as the denominator) – then a new baseline should be set by selecting the minimum of the latest consecutive pair of values that are *stable* (ie, within 40% of each other).

8.2.6 Other Safety Assessments

Variables for pregnancy testing and viral serology are shown in Table 10 and Table 11, respectively.

Table 10 Pregnancy and Hormone Testing

• Human-beta chorionic gonadotrophin (b-HCG) [a]	• Follicle-stimulating hormone (FSH)

[a] Sampling must follow the following specifications: Serum b-HCG test at the screening visit, at the last follow-up visit and at the ED visit; urine pregnancy at all other visits.

Table 11 Viral Serology

• Human immunodeficiency virus (HIV) I and II	• Hepatitis C RNA
• Hepatitis B surface antigen (HbsAg)	

COVID-19 testing

PCR or an alternative site-specific COVID-19 test will be conducted subject to local availability and study centre guidance.

Injection Site Reactions

Injection site reactions will be monitored at all visits and detailed information regarding symptoms etc will be collected on a specific eCRF page. Data to be captured include:

- Redness/erythema
- Swelling
- Itching/pruritus
- Pain or tenderness
- Induration
- Discoloration

Photo documentation of the ISR is recommended. If photo documentation is not available, all injection site reactions need to be described in detailed text, eg, definition, morphology, location, extent.

Vision

Effects on vision and night blindness will be monitored by analysing retinol, retinol binding protein (refer to lab panel in Section 8.2.5) and ordinary AE reporting.

8.3 Adverse Events and Serious Adverse Events

The PI is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE, AESI, and SAE can be found in Appendix B.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected starting at Visit 3, continuing throughout the treatment period, during the follow-up period and ending with Visit 24.

SAEs will be recorded from the time of signing of the ICF (ie, Visit 1 and onward).

If the investigator becomes aware of an SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a participant they themselves treated, the investigator shall, without undue delay, report the SAE to the sponsor within 24 hours.

8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse event variables

The following variables will be collected for each AE;

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the IP(s) (yes or no)
- Action taken with regard to IP(s)
- AE caused participant's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE

- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.3.3 Adverse Events of Special Interest

The following are considered AESI:

- Platelet count reduction
- Liver toxicity (transaminase elevations)
- Pro-inflammatory events
- Injection site reactions

8.3.4 Causality Collection

The investigator should assess causal relationship between IP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

8.3.5 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.6 Adverse Events Based on Examinations and Tests

The results from the CSP-mandated laboratory tests and vital signs will be summarised in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs ECGs should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the IP or are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or study intervention interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3.7 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN may need to be reported as SAEs. Please refer to Table 6 and Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.3.8 Reporting of Serious Adverse Events

All SAEs must be reported, whether or not considered causally related to the IP or to study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day (ie, immediately or **no later than 24 hours** after they become aware of it).

The designated AstraZeneca representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day (ie, immediately or **no later than 24 hours** after they become aware of it).

Once the investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the investigator/study site staff how to proceed.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug.

8.3.9 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study intervention.

8.3.9.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day** (ie, immediately or **no later than 24 hours** after they become aware of it).

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.8) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

When the eCRF module is used, include the following: The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

8.3.10 Medication Error, Drug Abuse, and Drug Misuse

8.3.10.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **one calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **one** (initial fatal/life-threatening or follow-up fatal/life-threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 8.3.8) and **within 30 days** for all other events.

8.3.10.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication error can be found in Appendix B 4.

8.3.10.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

8.3.10.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 4.

8.4 Overdose

For this study, any dose of AZD2693 greater than the dose intended to be given will be considered an overdose.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an IMP or AstraZeneca NIMP occurs in the course of the study, the investigator or other site personnel inform appropriate AstraZeneca representatives immediately but **no later than 24 hours** after they become aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within one or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.8) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study-specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- PK samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - PK samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterisation of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

8.5.1 Pharmacokinetics

- Plasma samples will be collected for measurement of plasma concentrations of total full length ASOs of AZD2693 as specified in the SoA (Section 1.3). On visits where IP is being administered *and* plasma samples are collected, timing of pre-dose and post-dose sampling must follow the following specifications:
  - Predose sampling on Visits 5, 11, 13, 15, 18, and 21
  - 2-hour post-dose sampling on Visits 3 and 13
- Samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the sponsor (eg, for safety reasons). The timing of sampling may be altered during the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.
- Plasma samples will be used to analyse the PK of AZD2693. Samples collected for analyses of AZD2693 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentration in plasma will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

8.5.2 Immunogenicity Assessments

Blood samples for determination of ADA in plasma will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. A tiered testing scheme will be employed, with the first step being screening. Samples found positive in the screening step will be tested in the confirmatory step. Samples confirmed positive for ADA in the confirmatory step will undergo endpoint titre determination. No additional collection of ADA samples is planned from ADA-positive participants after the last study visit.

Samples must be taken prior to dose administration on the indicated visits as detailed in the SoA (Section 1.3). Full details of the methods used will be described in a separate report.

ADA data that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

ADA samples may also be further tested for characterisation of the ADA response. Currently, no further evaluation of ADA's neutralising activity via a neutralising antibody assay is planned.

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

8.5.3 Pharmacodynamics

8.5.3.1 Collection of Samples

Biosamples will be collected as specified in the SoA (Section 1.3).

For storage, re-use, and destruction of PD samples see Appendix C.

8.5.4 Liver Biopsy

Liver biopsy samples will be taken at timepoints specified in the SoA (Section 1.3). Details of liver biopsy procedure are described in the Histopathology Manual.

Historical liver biopsy tissue obtained within 6 months of randomisation showing definitive NASH and fibrosis staging according to inclusion criteria must be sent for central reading to confirm diagnosis and fibrosis staging. If the historical biopsy is of poor quality, a new biopsy sample should be taken. For those participants without a historical biopsy, or when a new biopsy is being taken due to a poor quality historical one, investigators should determine eligibility for liver biopsy based on local procedures and clinical judgement during the screening period. This should include the use of non-invasive techniques such as imaging (eg, Fibroscan) and/or serum biomarker tests. Interpretation of the results is the responsibility of the investigator. The participants should meet all other inclusion criteria and none of the exclusion criteria.

Prior to performing the liver biopsy both at screening visit, where applicable, and at Visit 22, the investigator must ensure that the participant has no contraindications to the procedure and that there is no evidence of hepatic decompensation or coagulopathy. Recent (within the last 2 weeks, provided the participant's condition has remained stable) INR and platelet counts results must be available before the liver biopsy is performed; if not available, the coagulation parameter tests should be repeated. Liver biopsy should not be performed if any of the following are present:

- INR > 1.3.

- Platelet count < 100×10^9/L
- Any clinical signs on hepatic decompensation, including hepatic encephalopathy, ascites, variceal bleeding.

Participants may not undergo biopsy if they have recently used drugs that may affect coagulation and bleeding (including warfarin, heparin, aspirin, antiplatelets and NSAIDs) within time frames specified per local guidance and at the discretion of the treating physician.

Liver biopsy will be performed according to local procedures by the investigator or a qualified and experienced designee. When performing a needle biopsy, a 16G or larger cutting needle (eg, TruCut or Bard) should be used to obtain a 2 to 3 cm core of tissue from the right lobe of the liver. Use of suction needles should be avoided. In the event that a 2 to 3 cm core of tissue is not obtained from the biopsy, see the Histopathology Manual for guidance. If a historical biopsy used for eligibility was taken from the left lobe, then the biopsy occurring at Visit 22 should also be taken from the left lobe.

The resulting liver biopsy tissue should be processed for FFPE following local procedures.

In the case of a previously completed biopsy as standard of care, tissue blocks and/or additional slides from the original biopsy should be obtained according to central reading laboratory procedures to determine eligibility. FFPE-preserved liver tissue remaining after histopathology assessments will be used for exploratory research as described under exploratory objectives.

8.6 Human Biological Sample Biomarkers

8.6.1 Previously Characterised *PNPLA3* I148M Status

Previously characterised *PNPLA3* I148M status will be collected if available. This may be from research, local testing, or commercially available laboratory testing.

8.6.2 Collection of Mandatory Samples for Biomarker Analysis

Samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA (Section 1.3).

Biomarker samples are:

- Blood for PK and efficacy analyses
- Blood and buccal samples for identifying *PNPLA3* genotypes and CCI [redacted] CCI [redacted]
- Blood for hepatic health, inflammatory, and fibrosis biomarkers; samples to be taken prior to dose administration during the visits specified in the SoA (Section 1.3)
- Blood for diabetes/metabolic syndrome and renal biomarkers

- Blood for lipid biomarkers; samples to be taken prior to dose administration during the visits specified in the SoA (Section 1.3)
- Blood sample for analysis of plasma derived cell-free DNA will be collected as specified in the SoA (Section 1.3)
- Liver biopsy

Samples will be tested for markers of efficacy, safety, comorbidities, and PK to evaluate their association with the observed clinical responses to AZD2693.

The blood and buccal swab sample for *PNPLA3* I148M genotyping will be obtained from the participants at Visit 1 (during the early genotyping assessment). Participants must have completed the *PNPLA3* genotyping prior to start of Screening Visit 2 collection or submission of any samples or assessments. This sample is required to investigate the presence of the *PNPLA3* 148M variant that is needed to include a participant in the study CCI [redacted]. The results of the mandatory *PNPLA3* I148M genotyping for eligibility will be returned to the PI. The genotype will not be returned to the participant unless required by local law. The PI will be responsible to provide participants general education about *PNPLA3*.

8.6.3 Collection of Optional Biomarker Samples

Collection of optional samples for biomarker research is also part of this study as specified in the SoA (Section 1.3) and is subject to agreement to optional consent. Samples must be taken prior to dose administration on indicated visits.

Blood samples will be collected for future research. Participation is optional.

Samples will be tested for biomarkers and mechanisms that may affect PK, PD, safety, and tolerability to evaluate their association with the observed clinical responses to AZD2693.

8.6.4 Other Study-Related Biomarker Research

Already collected samples may be analysed on different biomarkers thought to play a role in NASH, PNPLA3 pathways or CV, metabolic, renal, and other conditions. Possible samples include but are not limited to serum analytes and liver tissue biomarkers to evaluate their association with observed clinical responses to AZD2693 treatment or among various genotypes.

For storage, re-use and destruction of biomarker samples see Section 8.5.

8.7 Optional Genomics Initiative Sample

Collection of optional blood samples for Genomics Initiative research is also part of this study as specified in the SoA (Section 1.3) and is subject to agreement in a separate ICF.

Blood samples for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in the optional genetic research may still participate in the study.

See Appendix D for information regarding the Genomics Initiative genetic sample. Details on processes for collection and shipment and destruction of these samples can be found either in the appendices or in the Laboratory Manual.

For storage and destruction of genetic samples see Appendix D.

8.8 Health Economics OR Medical Resource Utilisation and Health Economics

This section is not applicable.

8.9 Patient-Reported Outcome Questionnaires

PROs refer to all outcomes and symptoms that are directly reported by the participant. PROs have become important endpoints for regulatory and reimbursement authorities when evaluating effectiveness of treatment in clinical trials.

The following PROs will be administered: NASH-CHECK, SF-36v2 (acute recall), and PGIS for NASH (Appendix I). Participants will be asked to complete the questionnaires on an electronic device at site visits specified in the SoA (Section 1.3). A web back-up solution will be available.

The following best practice guidelines should be followed:

- PRO questionnaires should be completed before any other study procedures, to avoid bias when responding to questions.
- Site personnel must show participants how to use the electronic PRO device, in accordance with the instructions provided.
- Only assigned and trained personnel should show participants how to complete the ePRO. At each site, at least 2 staff members per device should be adequately trained for this task.
- Participants must not receive help from relatives, friends, or site staff to answer or to clarify PRO questions.
- If participants have any medical problems, they should discuss them with their doctor or research nurse separately from the PRO assessment.

- A key aspect of study success is to have high PRO compliance. Therefore, it is essential that site personnel follow the SoA (Section 1.3) and ensure that the device is charged and set up properly before the first participant comes for PRO baseline visit (Visit 3), in order to minimise missing data.
- Site staff must remind participants there are no right or wrong answers, and that the value and relevance of PRO data are to hear directly from participants, without interpretation from anyone else, how they function and feel.
- On completion of the questionnaires, the tablet should be handed back to a designated staff member, who should check that all questionnaires relevant for the specific visit (Section 1.3) were completed. If any PRO questionnaire was not completed, the site personnel must document the reason why a participant could not complete assessments in the eCRF.

NASH-CHECK

NASH-CHECK is a disease-specific PRO instrument assessing symptoms and health-related quality of life for participants with NASH (Doward et al 2021). NASH-CHECK (Appendix I 1) includes 28 items with a recall of the past 7 days. NASH-CHECK scores include 5 single-item symptom scores assessing Abdominal Pain, Abdominal Bloating, Fatigue, Sleep, and Itchy Skin; 1 symptom scale assessing Cognitive Symptoms (4 items); and 3 health-related quality of life scales assessing Activity Limitations (8 items), Emotional Impact (4 items) and Social Impact (7 items).

SF-36

The SF-36 health survey, version 2 (acute recall) (SF-36v2; Appendix I 2) is a 36-item self-report survey of functional health and well-being, with a 1-week recall period (Maruish 2011). Responses to 35 of the 36 items are used to compute an 8-domain profile of functional health and well-being scores. The remaining item, referred to as the 'Health Transition' item, asks participants to rate how their current state of health compared to their state of health 1 week ago, and is not used to calculate domain scores. The 8-domain profile consists of the following subscales: Physical Functioning, Role Limitations due to Physical Health, Bodily Pain, General Health Perceptions, Vitality, Social Functioning, Role Limitations due to Emotional Problems and Mental Health. Psychometrically-based physical and mental health component summary scores are computed from subscale scores to give a broader metric of physical and mental health-related quality of life.

PGIS

The PGIS (Appendix I 3) measures the participant's overall perceptions of their NASH-related symptoms. The PGIS is a static, single-item measure: 'How would you describe the severity of the symptoms you have experienced with your fatty liver disease (known as NASH) over the past 7 days?' The PGIS has 4 response options: "no symptoms," "mild," "moderate-" and "severe."

Participant Qualitative Interviews

Participants in the US (might be expanded to other countries as well) who provide their consent for participation in in-trial interviews will be invited to participate in an optional qualitative participant interview sub-study. Up to 46 participants will be enrolled in the sub-study, which consists of 2 one-on-one interviews in accordance with the SoA (Section 1.3) to characterise their experience of the disease and treatment.

Interviews will be conducted by an AstraZeneca vendor via telephone using a semi-structured interview guide. With prior participant consent, participant contact information will be provided to the AstraZeneca vendor to schedule and conduct the interviews. Both interviews will last approximately 45 minutes and will be audio-recorded with the participant's prior consent. The interviewer will have no prior knowledge of which study arm a participant has been assigned to. Interview format will be uniform irrespective of study arm.

During the first interview, participants will be asked a series of open-ended questions about their disease journey and disease experience; during the second interview, they will be asked about their experience of treatment, their impression and meaningfulness of treatment benefit and perception of risks. As necessary, probes may be included as part of the interview to elicit more detailed information. Rating scales may also be used.

Interview transcripts will be developed for qualitative analysis. The sponsor will have access to de-identified transcripts but not to the interview recordings. Transcripts will be de-identified and coded using a qualitative analysis software tool. All qualitative data will be stored on the vendor's secure server in a password-protected file. Due to the exploratory and qualitative nature of the data and analysis, the results will be presented in a separate report (not the CSR) and the data (transcripts) will not be entered into the study database. No identifiable data will be reported.

AstraZeneca will follow standard procedures for handling AE reporting involving these participants (as described in Section 8.3 and Appendix B). At the beginning and end of each interview, participants will be advised to report any AE to the Investigator or designee.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary objective is to demonstrate superiority of AZD2693 compared to placebo on the resolution of NASH without worsening of fibrosis after Week 52.

The summary measure for the primary endpoint will be proportion of responders. Primary endpoint will be analysed using a Cochran-Mantel-Haenszel test with stratification by T2DM presence and F2/F3 fibrosis stages based on the FAS population.

To strongly control the familywise error rate at the 0.05 level, the alpha expenditure of 0.05 (2-sided) will be allocated to the hypotheses for AZD2693 versus pooled placebo starting with the highest dose and going down when applicable for primary endpoint (homozygous only population).

9.2 Sample Size Determination

Up to approximately 4000 participants are estimated to be screened, based on estimated global NASH prevalence together with *PNPLA3* risk allele population. The study will randomise up to approximately 180 participants, The randomisation of 180 homozygous participants supports the evaluation of the primary endpoint. Participants homozygous for the *PNPLA3* rs738409 148M risk allele will be randomised in a 2:2:1:1 manner to receive two doses of AZD2693 or corresponding injection volumes of placebo.

For participants homozygous for the *PNPLA3* rs738409 148M risk allele, about 60 participants in each AZD2693 dose arm and about 60 participants in pooled placebo arm will provide more than 90% power for the test of each dose versus placebo to detect a difference of 35% in NASH resolution without worsening of fibrosis assuming a response rate to placebo of 20%. The calculations assume a 2-sided alpha level of 0.05.

At randomisation, participants will be stratified by the presence/absence of T2DM and by fibrosis stage F2/F3.

9.3 Populations for Analyses

The populations/analysis sets are defined in Table 12.

Table 12 Populations for Analysis

Population/Analysis set	Description
Enrolled	All participants who sign the ICF.
Randomly assigned to study intervention	All participants homozygous for the risk allele randomised into the study.
Safety analysis set	All participants homozygous for the risk allele randomised into the study who have received at least one dose of study intervention. Participants will be analysed according to the treatment they actually received.
Full analysis set	All participants homozygous for the risk allele randomised to study intervention and received at least one dose of study intervention. Participants will be analysed according to the treatment they were randomised to.
PK analysis set	All participants homozygous for the risk allele randomised into the study who have at least one measured plasma concentration of AZD2693 full-length ASO.
ADA set	All participants homozygous for the risk allele randomly assigned to study treatment and who take at least 1 dose of study treatment and had at least one

Table 12 Populations for Analysis

Population/Analysis set	Description
	ADA assessment available. Participants will be included in the analysis according to the treatment to which they were randomised
Safety analysis set, Heterozygous participants	All participants heterozygous for the risk allele randomised into the study who have received at least one dose of study intervention. Participants will be analysed according to the treatment they actually received.
Full analysis set, Heterozygous participants	All participants heterozygous for the risk allele randomised to study intervention who received at least one dose of study intervention. Participants will be analysed according to the treatment they were randomised to.

ADA, anti-drug antibody; ASO, antisense oligonucleotide; ICF, informed consent form.

9.4 Statistical Analyses

The SAP will be finalised prior to Data Base Lock and it 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, secondary, and tertiary/exploratory endpoints.

Planned statistical analyses include:

- A primary analysis after the treatment period. The primary analysis will be performed when all participants have completed the treatment period and last biopsy. Key efficacy and safety/tolerability data will be assessed. The design or the conduct of this study will not be impacted by the primary analysis results. The primary analysis will be performed by an unblinded team. The study team will remain blinded until the end of the follow-up.
- A complete analysis after the final follow-up (after Data Base Lock).

9.4.1 General Considerations

Analysis will use 2-sided 5% significance levels (equivalent to 1-sided 2.5% significance levels) unless otherwise stated.

In general, the baseline value for statistical analysis is the last non-missing value prior to administration of the first dose of study intervention. Details are described in the SAP.

Participant disposition will be summarised.

Participants and/or data excluded from the analysis set will be listed along with reasons for exclusion.

Demographic variables (age, gender, race, ethnicity, height, weight, and BMI) will be listed by participant. Demographic characteristics (age, gender, race, and ethnicity) and participant characteristics (height, weight and BMI) will be summarised by treatment (dose level of AZD2693 and pooled placebo) for each population.

A more comprehensive description of statistical procedures and assessments will be available in the SAP.

9.4.2 Efficacy

Analysis will use 2-sided 5% significance levels (equivalent to 1-sided 2.5% significance levels) unless otherwise stated. The participants from the dose-matched placebo groups will be combined for analysis into a single placebo group.

The primary estimand of interest for the primary and other histological endpoints will be a hybrid of the treatment policy strategy with the composite strategy. Under this approach, a composite strategy is applied to the histological endpoints for intercurrent events of liver outcomes (adjudication events of hepatic decompensation, clinical cirrhosis, DILI, hepatocellular carcinoma, and death [further defined in the CEA charter]) and treatment policy applies to intercurrent events of treatment discontinuation, deviations from the protocol dosing schedule, changes in background medication, or use of prohibited medication or other protocol deviations. Only the treatment policy strategy will be used to handle the intercurrent events for other efficacy endpoints.

Under the composite strategy, all events occurring from randomisation to Week 52 or prior to the post-randomisation biopsy will be used to define the analysis variables (further details in the SAP).

Participants will be analysed according to their randomised study intervention assignment, irrespective of the treatment they actually received. The FAS will include all randomised and treated participants who received at least one dose of IP irrespective of their protocol adherence, addition or modification of background medications, discontinuation of study intervention or switches to alternative medications, and continued participation in the study. The FAS will be considered the primary analysis set for the primary and secondary variables and for the exploratory efficacy variables.

All efficacy data collected for PD will be listed for each participant and summarised descriptively (including, but not limited to, mean, standard deviation, minimum, median, maximum, geometric mean, geometric coefficient of variation) by treatment and timepoint/visit. Figures of the mean response (absolute change from baseline, and value relative to baseline where appropriate) will be used to visualise the average PD response over time.

Liver histological endpoints are:

- NASH resolution without worsening of liver fibrosis (primary endpoint).
- Liver fibrosis improvement with no worsening of NASH.

Liver biopsy will be performed at baseline and after 52 weeks of treatment to assess the effect of AZD2693 on NASH histopathological features compared with placebo. The use of historical (up to 6 months before randomisation) liver biopsy will be allowed as baseline measurement. Central reading is required for all liver biopsy data (including historical).

9.4.2.1 Primary Endpoint(s)

The primary objective is to demonstrate superiority of AZD2693 compared to placebo on the resolution of NASH without worsening of fibrosis after Week 52 in participants homozygous for the *PNPLA3* rs738409 148M risk allele.

To support the primary objective, the primary endpoint is

- The resolution of NASH without any worsening of fibrosis (yes/no).
  - The resolution of NASH is defined as a ballooning score of 0, inflammation score of 0 to 1 and steatosis score of any degree (from 0 to 3), as assessed by NASH CRN/NAS score.
  - Worsening of fibrosis is defined as an increase in the NASH CRN fibrosis score.

The summary measure for the primary endpoint will be proportion of responders. The primary endpoint will be analysed using a Cochran-Mantel-Haenszel test with stratification by T2DM presence and F2/F3 fibrosis stages based on the FAS population. The treatment effects will be summarised by the difference in proportions, 95% confidence interval and p-value.

To strongly control the familywise error rate at the 0.05 level, the alpha expenditure of 0.05 (2-sided) will be allocated to the hypotheses for AZD2693 versus pooled placebo starting with the highest dose and going down for primary endpoint (homozygous only population). Final multiplicity plan will be described in the SAP.

9.4.2.2 Secondary Endpoint(s)

For participants homozygous for the *PNPLA3* rs738409 148M risk allele, secondary endpoints are:

- Key secondary: At least one stage of liver fibrosis improvement with no worsening of NASH (yes/no) after 52 weeks (worsening defined as an increase of at least one stage of either lobular inflammation or hepatocyte ballooning or steatosis according to NASH CRN criteria)
- Improvement in fibrosis by at least one stage based on biopsy after Week 52

- ≥ 2-point improvement in NAS after 52 weeks

In general, statistical analyses will consist of the comparison between active and placebo. Multiple testing adjustment will only be applied to the key secondary endpoint. Binary endpoints will be analysed using the same Cochran-Mantel-Haenszel approach as for the primary endpoint. Participants with missing final histology data will be assumed to be non-responders. Where applicable, the analyses of the change from baseline variables will each utilise a repeated measures model with fixed effects of baseline value, presence of T2DM, fibrosis stage (F2/F3), week, treatment and interaction of treatment and week. An unstructured covariance structure will be used in the model as a first option. No explicit imputation of missing values will be made for these repeated measures models. Further specifications of the analyses are described in the SAP.

Exploratory endpoints are:

- Resolution of NASH with at least one stage of liver fibrosis improvement (yes/no) after 52 weeks in homozygous carriers of the *PNPLA3* rs738409 148M risk allele
- Change from baseline to post-Week 52 in:
  - NAS (0-8)
  - Stage of fibrosis according to the Kleiner fibrosis classification (0-4)
  - Activity component of SAF score (0-4)
  - ALT, AST, GGT
  - CK-18 (M65 and M30)
  - ProC3
  - ELF score
  - Total cholesterol
  - LDLc
  - HDLc
  - Triglycerides
  - FIB-4
  - NIS4
  - HbA1c
  - Insulin
  - c-Peptide
  - Plasma glucose
  - HOMA-IR

- eGFR
- FFA
- APRI
- NFS
- ApoB
- *PNPLA3* protein measured by IHC
- Liver stiffness
- HFF
- Volume corrected HFF
- Liver fat volume

In general, statistical analyses will consist of the comparison between active treatment and pooled placebo. Multiple testing adjustment will not be applied to the exploratory endpoints.

The analyses will compare the efficacy of AZD2693 to placebo. Where applicable, binary endpoints will be analysed using the same Cochran-Mantel-Haenszel approach as for the primary endpoint. Participants with missing final histology data will be assumed to be non-responders. Where applicable, the analyses of the change from baseline variables will each utilise a repeated measures model adjusting for baseline value, presence of T2DM, fibrosis stage (F2/F3), week, treatment and the interaction of treatment and week. An unstructured covariance structure will be used in the model as a first option. No explicit imputation of missing values will be made for these repeated measures models. Further specifications of the analyses are described in the SAP.

Pharmacokinetic analyses

Pharmacokinetic blood collection times will be listed. Plasma concentrations will be summarised by treatment (dose level of AZD2693) for each population and sampling time point, using descriptive statistics based on the PK analysis set and included in the CSR.

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

If data permits, all clinical PK data for this drug product – possibly including previous PK data from SAD and MAD studies – may be used for population PK analysis. Furthermore, the population PK model may be coupled with separate PD models for description of exposure response of key biomarkers, clinical endpoints, and potential safety variables. The results of any such modelling activity will be provided in a separate report (as an appendix to the CSR or as a stand-alone report).

Immunogenicity

Development of ADA will be monitored for each participant; analysis and reporting of data related to ADA will be specified in the SAP.

9.4.3 Safety

All safety analyses will be performed using the safety analysis set. Safety data will be summarised descriptively and will not be formally tested.

All safety data will be presented in the data listings. In addition, renal safety biomarkers, platelet count and liver biochemistry parameters (ALT, AST, bilirubin) will be presented graphically by treatment (dose level of AZD2693 and pooled placebo).

AEs will be coded using the most recent version of MedDRA vocabulary. AEs will be presented for each treatment group by System Organ Class and/or Preferred Term covering number, percentage of participants and number of events where appropriate.

The summaries will include AEs, SAEs and DAEs. AEs by severity and causally related AEs will also be presented.

Furthermore, listings of SAEs, Deaths and DAEs will be made.

Tabulations and listings of data for vital signs and clinical laboratory tests will be presented. Results from safety and ECGs will be presented in tables and listings. Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Out-of-range values for safety laboratory tests will be flagged in individual listings as well as summarised descriptively.

9.5 Interim Analyses

No interim analysis is planned for this study.

9.6 Data Monitoring Committee

An iSMC will be formed to perform continuous safety monitoring according to the iSMC charter. Details of the continuous safety monitoring will be specified in the iSMC charter. The role and the primary responsibilities of the iSMC members will be described in the committee charter. For details on the iSMC, refer to Appendix A 5.

The study will engage an independent, external CEA committee to independently review, interpret and adjudicate potential CV and liver events experienced by the participants. The CEA committee members will not have access to individual treatment codes for any

participant. The precise responsibilities and procedures applicable for CEA will be detailed in the CEA charter.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

The emergence of the COVID-19 presents a potential safety risk for participants. As the threat of pandemic burden (including new outbreaks, locally or globally) may impact the further conduct of clinical studies, appropriate risk assessments and mitigation measures will need to be taken into consideration to protect participants, site staff, communities at large and society as a whole. Sites should follow their local rules, regulations, and guidelines when urgent or emergent changes need to be taken into consideration as a result of COVID-19 risk increase and implement appropriate mitigations. The sponsor should be kept informed and should perform a risk assessment, and then identify mitigations and agree measures to prioritise participants' safety as well as data validity.

Compliance with the study protocol should be ensured to such an extent that an ongoing benefit-risk assessment for the clinical study and its participants is still possible.

All confirmed and suspected COVID-19 infections events must be recorded in the eCRF.

Please refer to Appendix J for further details.

Appendix A Regulatory, Ethical and Study Oversight Considerations

A 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 Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, revised protocol, ICF, Investigator Brochure, and other relevant documents (eg, 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 revised protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO, but the accountability remains with AstraZeneca.
- The investigator will be responsible for 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), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to AstraZeneca of a 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.
- AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. AstraZeneca will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- In the EU, AstraZeneca will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU) No 536/2014. All SUSARs to investigational medicinal product will be reported to the EudraVigilance database within the required regulatory timelines.
- For all studies except those utilising medical devices, investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

- Adherence to European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from AstraZeneca will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches of Protocol or GCP

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. Where the EU Clinical Trials Regulation 536/2014 applies, AstraZeneca has in place processes to enter details of serious breaches into the European Medicines Agency (EMA) Clinical Trial Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:
  - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach.
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

A 2 Financial Disclosure

Investigators and sub-investigators will provide AstraZeneca with sufficient, accurate financial information as requested to allow AstraZeneca 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.

A 3 Informed Consent Process

- The investigator or their representative will explain the nature of the study to the participant or their legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- If new information requires changes to the ICF, consider if participants must be re-consented and if so, this must be to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 90 days from the previous ICF signature date.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The investigator or authorised designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

A 4 Data Protection

- Participants will be assigned a unique identifier by AstraZeneca. Any participant records or datasets that are transferred to AstraZeneca will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by AstraZeneca in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by AstraZeneca, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The participant must be informed that data will be collected only for the business needs. We will only collect and use the minimum amount of personal data to support our

business activities and will not make personal data available to anyone (including internal staff) who is not authorised or does not have a business need to know the information.

- The participant must be informed that in some cases their data may be pseudonymised. The General Data Protection Regulation (GDPR) defines pseudonymisation as the processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

Personal Data Breaches

A 'personal data breach' means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, personal data transmitted, stored, or otherwise processed.

- In compliance with applicable laws, the Data Controller[1] for the processing activity where the personal data breach occurred (AstraZeneca or respectively the site), will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.
- Whilst AstraZeneca has processes in place to deal with personal data breaches it is important that investigators that work with AstraZeneca have controls in place to protect participant data privacy.

The Investigator should have a process in place to ensure that:

- allow site staff or service providers delegated by the investigator/institution to identify the occurrence of a (potential) personal data breaches.
- Any (potential) personal data breach is promptly reported to AstraZeneca or delegated party, through the contacts (e-mail address or telephone number) provided by AstraZeneca.

AstraZeneca and the site must demonstrate that they:

- have taken all necessary steps to avoid personal data breaches and
- have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (eg, applying encryption, maintaining and keeping systems and IT security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).

[1] The **data controller** determines the **purposes** for which and the **means** by which personal data is processed, as defined by the European Commission

- where possible, have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.
- where it has not been possible to develop an internal data breach reporting and investigation process, the site follows AstraZeneca's instructions.

Notification of personal Data Breach to participants:

- Notification to participants is done by the site for the data breaches that occurred within the processing activities for which the site is the Data Controller and for data breaches occurred within the processing activities of AstraZeneca as the Data Controller , the notification is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of AstraZeneca, so that AstraZeneca has no access to the identifying personal information of the participants. The site and/or Principal Investigator shall conduct the notification by contacting the participants using the information that they gave for communication purposes in clinical research.
- If a personal data breach occurs in a processor's systems, engaged by AstraZeneca, the processor under contractual obligations with AstraZeneca promptly and in due course after discovering the breach notifies AstraZeneca and provides full cooperation with the investigation. In these cases, to the extent AstraZeneca is the Data Controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to participants. If the personal data breach needs to be notified to the participants, the notification to participants is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of the sponsor, so that AstraZeneca has no access to the identifying personal information of the participants.
- If a personal data breach involving an AstraZeneca's representative device (ie, Study Monitor laptop), AstraZeneca representative will provide AstraZeneca with all of the information needed for notification of the breach, without disclosing data that allows AstraZeneca directly or indirectly to identify the participants. The notification will be done by AstraZeneca solely with the information provided by the Study Monitor and in no event with access to information that could entail a risk of re-identification of the participants. If the data breach must be notified to the data subjects, the notification will be done directly by the Study Monitor in collaboration with the site and/or Principal Investigator, acting on behalf of the sponsor, so that AstraZeneca has no access to the identifying personal information of the participants. The contract between AstraZeneca and the Study Monitor shall expressly specify these conditions.
- The contract between the site and AstraZeneca for performing the clinical research includes the provisions and rules regarding who is responsible for coordinating and directing the actions in relation to the breaches and performing the mandatory notifications to authorities and participants, where applicable.

A 5 Committees Structure

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the CSP and letters to investigators.

Event Adjudication Committee

An Event Adjudication committee is to be established to provide an independent, external, systematic, and unbiased assessment of major CV and liver safety events for the study.

The role and the primary responsibilities of the EA committee members, as well as the purpose and timing of EA meetings are described in the EA charter. The EA will provide review independent of AstraZeneca, the study clinical team and all other individuals associated with the conduct of the study.

Data Monitoring Committee

An independent internal SMC will be formed to perform continuous safety monitoring according to the iSMC charter. The role and primary responsibilities of the iSMC members will be described in the committee charter.

A 6 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on www.astrazenecaclinicaltrials.com, http://www.clinicaltrials.gov, and https://euclinicaltrials.eu, as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the AstraZeneca or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- Quality tolerance limits (QTLs) will be predefined in the Integrated Quality Risk Management Plan (IQRMP) to identify systematic issues that can impact participant 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 summarised in the CSR.
- Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are included in the Monitoring Plan.
- AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Monitoring Plan.
- AstraZeneca or designee is responsible for the data management of this study including quality checking of the data.
- AstraZeneca assumes accountability for actions delegated to other individuals (eg, Contract Research Organisations).
- Study monitors will perform ongoing source data verification as per the Monitoring Plan to confirm that data entered into the eCRF by authorised 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.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global Retention and Disposal (GRAD) Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to the AstraZeneca.

A 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 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 can be found in the sources data agreement and computerised data check list for electronic source data.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

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

The investigator may 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:

- 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 recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multi-centre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of Serious Adverse Events

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death.
- Is immediately life-threatening.
- Requires in-patient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse Events (AEs) for **malignant tumours** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-SAE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability, or incapacity but may jeopardise the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

Intensity Rating Scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for

several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgement. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related.'

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- Occurred
- **Was identified and** the participant received the drug
- Did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, eg, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which led to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the Data Entry Site (DES) using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each study site keeps full traceability of collected biological samples from the participants whilst in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples whilst in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

All appropriately consented samples will be retained for maximum 15 years from last subject last visit.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.

- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A Pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

Appendix D Optional Genomics Initiative Sample

D 1 Use/Analysis of DNA

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments, or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participant's DNA, ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples collected and mentioned within this appendix will be part of the Genomics Initiative and for clarity, are not the samples required for mandatory *PNPLA3* I148M genotyping.

D 2 Genetic Research Plan and Procedures

Selection of Genetic Research Population

- All participants will be asked to participate in this genetic research. Participation is voluntary and if a participant declines to participate there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

Inclusion Criteria

For inclusion in this genetic research, participants must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol and provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion Criteria

- Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:
  - Non-leucocyte depleted whole blood transfusion in 120 days of genetic sample collection.
  - Healthy Volunteers and paediatric participant samples will not be collected for the Genomics Initiative.

Withdrawal of Consent for Genetic Research

- Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2 of the main Clinical Study Protocol.

Collection of Samples for Genetic Research

- The blood sample for this genetic research will be obtained from the participants at Visit 3. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the sample is not drawn at Visit 3 it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

Coding and Storage of DNA Samples

- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples will be stored for a maximum of 15 years, from the date of last participant last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached. CCI [redacted]
- An additional second code will be assigned to the sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).
- The link between the participant enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

- The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed Consent

- The genetic component of this study is optional, and the participant may participate in other components of the main study without participating in this genetic component. To

participate in the genetic component of the study the participant must sign and date both the consent form for the main study and the consent form for the Genomics Initiative component of the study. Copies of both signed and dated consent forms must be given to the participant and the original filed at the study centre. The Principal investigator(s) is responsible for ensuring that consent is given freely and that the participant understands that they may freely withdrawal from the genetic aspect of the study at any time.

Participant Data Protection

- AstraZeneca will not provide individual genotype results to participants, any insurance company, any employer, their family members, general physician unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a participant's identity and also have access to his or her genetic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

Data Management

- Any genetic data generated in this study will be stored at a secure system at AstraZeneca and/or designated organisations to analyse the samples.
- AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations, or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results but they will not be able to see individual participant data or any personal identifiers.
- Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

E 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

Specific guidance on managing liver anomalies can be found in Section 6.6 of the Clinical Study Protocol.

During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug-Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) $\geq 3 \times$ Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) $\geq 2\times$ ULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law

AST or ALT ≥ 3× ULN **together with** TBL ≥ 2× ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

E 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

Central Laboratories Being Used:

When a participant meets any of the PHL identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the investigator (also sent to AstraZeneca representative).

The investigator will also remain vigilant for any local laboratory reports where the PHL identification criteria are met, where this is the case the investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory without delay
- Complete the appropriate unscheduled laboratory eCRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the investigator will without delay:

- Determine whether the participant meets PHL criteria (see Section E 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria not met

If the participant does not meet PHL criteria the investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

E 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study intervention (see Section 1.3).
- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For participants that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition
- The Study Physician contacts the investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data
- Subsequent to this contact the investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the Hy's law lab kit should be used.
  - Complete the 3 Liver eCRF Modules as information becomes available.

[#]**A 'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the Study Physician if there is any uncertainty.

E 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF
- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Actions required When Potential Hy's Law Criteria are met Before and After Starting Study Intervention

This appendix is applicable to participants who meet potential Hy's Law criteria on study intervention, having previously met potential Hy's Law criteria at a study visit prior to starting study intervention.

At the first on-study intervention occurrence of potential Hy's Law criteria being met the investigator will determine if there has been a significant change in the participant's condition compared with the last visit where potential Hy's Law criteria were met

- If there is no significant change no action is required.
- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Appendix E 4.2.

E 7 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a participant meets PHL criteria on-study intervention and has already met PHL criteria at a previous on-study intervention visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

> Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study eg, chronic or progressing malignant disease, severe infection or liver disease or did the participant meet PHL criteria prior to starting study intervention and at their first on-study intervention visit as described in Section 6 of this Appendix?

If **No**: follow the process described in Section E 4.2 for reporting PHL as an SAE

If **Yes**: Determine if there has been a significant change in the participant's condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change[#] follow the process described in Section E 4.2 for reporting PHL as an SAE

[#] **A 'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the Study Physician if there is any uncertainty.

E 8 Laboratory Tests

Hy's Law Lab Kit for Central Laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV HBsAg IgM and IgG anti-HBc HBV DNA [a] IgG anti-HCV HCV RNA [b] IgM anti-HEV HEV RNA
Other viral infections	IgM and IgG anti-CMV IgM and IgG anti-HSV IgM and IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin) [c]
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin [c] Transferrin saturation

[a] HBV DNA is only recommended when IgG anti-HBc is positive

[b] HCV RNA PCR reflex test to be performed in participants with a positive or inconclusive Hepatitis C antibody titre

[c] CD-transferrin and Transferrin are not available in China. Study teams should amend this list accordingly

Appendix F Actions in Case of Development of Thrombocytopenia or Uninterpretable Platelet Counts After Administration of ASOs

In case of thrombocytopenia, platelet assessments will be performed at a local laboratory and/or at a central laboratory, as appropriate at the discretion of the PI. Results should be documented in source documents and eCRF.

Recommended actions include reassessment of platelet count, adjustment of monitoring frequency (platelet count $< 100 \times 10^9$/L), assessment of additional laboratory parameters (platelet count $< 75 \times 10^9$/L), referral to a haematologist (platelet count $\leq 50 \times 10^9$/L) and start of supportive treatment with corticosteroids (platelet count $\leq 30 \times 10^9$/L). **Study intervention discontinuation according to the defined stopping criteria is essential in participants with suspected thrombocytopenia.**

F 1 Actions in Case of Uninterpretable Platelet Count Results

Participants with uninterpretable platelet laboratory results due to clumping, haemolysis, or quantity not sufficient must be reassessed within 2 days. Dosing is not allowed to proceed until the investigator has determined that the results are within acceptable range according to the defined stopping criteria.

In a clinical study with the ASO inotersen, diagnosis and treatment of severe thrombocytopenia were delayed in some participants because of uninterpretable platelet counts due to clumping of platelets in the test tube. Platelet clumping in the test tube was most likely caused by a combination of ASO-induced antiplatelet immunoglobulin (Ig)G antibodies and the anticoagulant EDTA. If there is suspicion of EDTA-mediated platelet clumping, a repeat platelet count using a different anticoagulant, eg, sodium citrate or heparin, should be done as soon as possible and always before a new dose is given.

F 2 Thrombocyte Monitoring Frequency

Platelet count (per µL)	Monitoring frequency
$> 100 \times 10^9$/L	Monitoring as per Schedule of Activities (Section 1.3)
$> 100 \times 10^9$/L and more than 30% reduction from baseline	Every 2 weeks
$\geq 75 \times 10^9$/L to $< 100 \times 10^9$/L	Every week
$< 75 \times 10^9$/L	Intensified monitoring; twice weekly to daily monitoring dependent of platelet count and rate of decline

F 3 Additional Laboratory Assessments (Platelet Count < 75×10^9/L)

• Peripheral smear
• Fibrinogen split products or D-dimer on fresh blood
• Citrated sample for platelets Coagulation panel (PT/INR, APTT) CBC with reticulocytes and mean platelet volume (MPV)
• Serum B12 and folate
• Fibrinogen
• von Willebrand factor
• Total globulins, total immunoglobulins (Ig)A, IgG, and IgM
• Complement: total C3, total C4, Bb, C5a
• hs-CRP
• Serology for:
• HBV, HCV, HIV (if not done for screening)
• Rubella
• CMV
• EBV
• Parvo B19
• Helicobacter pylori (IgG serum test)
• Auto-antibody screen:
• Antiphospholipid
• Rheumatoid factor
• Anti-dsDNA
• Anti-thyroid
• To Be Performed at Specialty Lab(s):
• Antiplatelet antibodies and Anti-PF4 assay
• Anti-Drug antibody

F 4 Referral to Expert Haematologist Care

Participants that develop thrombocytopenia with platelet counts ≤ 50×10^9/L should be referred to a haematologist for diagnostic and therapeutic management. This may include the additional laboratory tests described in the Table above. Additional bone marrow aspiration and biopsy should be considered.

F 5 Supportive Treatment with Corticosteroids

Treatment of severe thrombocytopenia requires close communication among consulting specialists. **For major or life-threatening bleeding, platelet transfusions should be administered without delay.** Because ASOs have been associated with immune-mediated thrombocytopenia it is strongly recommended that participants with platelet counts ≤ 30×10^9/L receive glucocorticoid therapy (unless contraindicated). High dose steroids have

been reported to reverse platelet decline and accelerate platelet recovery. **Treatment guidelines for immune thrombocytopenia recommend** (Provan et al 2010): **Dexamethasone** 40 mg daily for 4 days every 2 to 4 weeks for 1 to 4 cycles; **Prednis(ol)one** 0.5 to 2 mg/kg/day for 2 to 4 weeks then taper; or Methylprednisolone 30 mg/kg/day for 7 days (note: may require continuation with oral steroids after methylprednisolone). Platelet count should be monitored closely during corticosteroid treatment. An increased or normalised platelet count is expected within 2 weeks of therapy. Once the platelet count normalises or rises significantly and plateaus > 50×10^9/L, no additional therapy is needed. **Participants should be followed until platelet count has been > 100×10^9/L for 1 month** (see above Table in Appendix F 2 for monitoring frequency).

Provan et al 2010
Provan D, Stasi R, Newland AC, Blanchette VS, Bolton-Maggs P, Bussel JB, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood. 2010;115(2):168-86.

Appendix G Guidance for Definition of Anaphylactic/Hypersensitivity Reactions and Checklist for the Investigator

The National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. They recognise 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to > 95% of all cases of anaphylaxis (for all 3 categories) [Romeo et al 2010].

- Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalised hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:
  - Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
  - Reduced BP or associated symptoms of end organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
- Two or more of the following that occur rapidly after exposure to a likely allergen for that participant (minutes to several hours):
  - Involvement of the skin-mucosal tissue (eg, generalised hives, itch-flush, swollen lips-tongue-uvula)
  - Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
  - Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
  - Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
- Reduced BP after exposure to known allergen for that participant (minutes to several hours):
  - Infants and children: low systolic BP (age-specific) or greater than 30% decrease in systolic BP
  - Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

HYPERSENSITIVITY REACTIONS – CHECKLIST FOR THE INVESTIGATOR

At least the following should be checked. If "YES" the diagnosis (preferably not symptoms) should be recorded as adverse event.

	YES	NO
Skin and subcutaneous events		
Urticaria		
Erythema		
Pruritus		
Face oedema		
Eye oedema		
Tongue swelling		
Angioedema		
Respiratory compromise		
Bronchospasm		
Dyspnoea		
Cough		
Choking		
Stridor		
Respiratory arrest		
Cardiovascular events		
Cardiac arrest		
Cardiovascular insufficiency		
Hypotension		

ADDITIONAL SAMPLES TO BE COLLECTED IN CASE OF AN ANAPHYLACTIC-LIKE REACTION

In case of anaphylactic-like reaction, the blood samples for tryptase assessments should be taken 30 minutes, 60 minutes, and 120 minutes after the onset of event, if feasible.

In addition, samples for analysis of ADA should be taken at the day of the anaphylactic-like reaction, if feasible.

Romeo et al 2010
Romeo S, Sentinelli F, Dash S, Yeo GS, Savage DB, Leonetti F, et al. Morbid obesity exposes the association between PNPLA3 I148M (rs738409) and indices of hepatic injury in individuals of European descent. Int J Obes (Lond). 2010;34(1):190-4.

Appendix H Tools for Histological Assessments of Non-alcoholic Steatohepatitis

The NIDDK NASH CRN system of grading disease activity and staging fibrosis separately is the most widely used and validated system for histological assessment of NASH in clinical trials (Kallwitz et al 2019, Kleiner et al 2005, Siddiqui et al 2018).

The non-alcoholic fatty liver disease activity score (NAS) is the sum of the separate scores for steatosis (0 to 3), hepatocellular ballooning (0 to 2), and lobular inflammation (0 to 3; Kallwitz et al 2019, Kleiner et al 2005, Sanyal et al 2011).

Non-alcoholic steatohepatitis fibrosis stages range from F0 to F4.

Description of non-alcoholic fatty liver disease activity score and NASH fibrosis stages:

NASH activity grade: grade = total score: S + L + B (range 0–8)					
Steatosis	S score	Lobular inflammation	L score	Hepatocyte ballooning	B score
< 5%	0	None	0	None	0
5–33%	1	< 2	1	Few ballooned cells	1
34–66%	2	2–4	2	Many ballooned cells	2
> 66%	3	> 4	3		

NASH fibrosis stage	Stage
None	0
Mild, zone 3 perisinusoidal fibrosis	1a
Moderate, zone 3 perisinusoidal fibrosis	1b
Portal/periportal fibrosis only	1c
Zone 3 perisinusoidal and portal/periportal fibrosis	2
Bridging fibrosis	3
Cirrhosis	4

B, Ballooning; L, Lobular; NASH, Non-alcoholic steatohepatitis; S, Steatosis.

Kallwitz et al 2019
Kallwitz ER, Tayo BO, Kuniholm MH, Cai J, Daviglus M, Cooper RS, et al. American ancestry is a risk factor for suspected nonalcoholic fatty liver disease in Hispanic/Latino adults. Clin Gastroenterol Hepatol. 2019;17(11):2301-9. doi:10.1016/j.cgh.2019.02.007.

Kleiner et al 2005
Kleiner DE, Brunt EM, van Natta M, Behling C, Contos MJ, Cummings OW et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology. 2005;41(6):1313-21. doi:10.1002/hep.20701.

Sanyal et al 2011
Sanyal AJ, Brunt EM, Kleiner DE, Kowdley KV, Chalasani N, Lavine JE et al. Endpoints and clinical trial design for nonalcoholic steatohepatitis. Hepatology. 2011;54(1):344-53. doi:10.1002/hep.24376.

Siddiqui et al 2018
Siddiqui MS, Harrison SA, Abdelmalek MF, Anstee QM, Bedossa P, Castera L, et al. Case definitions for inclusion and analysis of endpoints in clinical trials for nonalcoholic steatohepatitis through the lens of regulatory science. Hepatology. 2018;67(5):2001-12. doi:10.1002/hep.29607.

Appendix I Patient-Reported Outcomes Questionnaires

Minor format changes may be made to fit an electronic format.

I 1 NASH-CHECK

Patient Reported Outcomes questionnaires under copyrights.

Patient Reported Outcomes questionnaires under copyrights.

Patient Reported Outcomes questionnaires under copyrights.

Patient Reported Outcomes questionnaires under copyrights.

Patient Reported Outcomes questionnaires under copyrights.

I 2 SF-36v2

Patient Reported Outcomes questionnaires under copyrights.

Patient Reported Outcomes questionnaires under copyrights.

Patient Reported Outcomes questionnaires under copyrights.

Patient Reported Outcomes questionnaires under copyrights.

Patient Reported Outcomes questionnaires under copyrights.

Patient Reported Outcomes questionnaires under copyrights.

I 3 PGIS

PATIENT GLOBAL IMPRESSION OF SEVERITY – NASH

How would you describe the severity of the symptoms you have experienced with your fatty liver disease (known as NASH) over the past 7 days?

Please select one response only

- ☐ No symptoms
- ☐ Mild
- ☐ Moderate
- ☐ Severe

REVIEW COPY-NOT FOR ADMINISTRATION

Appendix J Coronavirus (COVID-19) Pandemic Guidance

J 1 Background to COVID-19

There is currently an outbreak of respiratory disease coronavirus disease 2019 (COVID-19) caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that was first detected in Wuhan City, Hubei Province, China in 2019. This new virus has rapidly spread across the globe causing the World Health Organisation to declare a pandemic situation on 12 March 2020. The countermeasures initiated by national and local governments worldwide and the recommendations issued by the health authorities have impacted current and new clinical studies. As the threat of pandemic burden including new outbreaks, locally or globally, may impact the further conduct of clinical studies, appropriate risk assessments and mitigation measures will need to be taken into consideration in all clinical studies to protect participants, site staff, and society as a whole.

Both the EMA) and FDA as well as national health authorities in Europe have issued new guidelines that aim to provide recommendations for actions for conduct of clinical studies of medical products during COVID-19 pandemic. Since the pandemic situation is evolving, guidelines, recommendations, national laws, and local restrictions may change at high pace. Given the circumstances of potentially relapsing pandemic or epidemic situation with regard to the spread of COVID-19 in future, special attention will be paid to protect participants participating in the study and site staff involved in the investigations against infection with SARS-CoV-2.

J 2 Risk Assessment for COVID-19 Pandemic

Mitigation measures will be implemented in the study to minimise the risk of exposure to infected people, this however cannot be completely excluded as the participants may need to expose themselves to public areas (eg, commute to the site) and have additional human contact (eg, with site staff and other participants of the clinical study). Measures to mitigate the additional risks caused by COVID-19 are:

- This study will start enrolling only when the sponsor and CRO in collaboration deem it is safe to start the study. In addition, the study will not start until the local confinement measures or other safety restrictions linked to the COVID-19 pandemic imposed by the local authorities are compatible with safe conduct of the study.
- Current national and state laws and local recommendations for prevention of pandemic will be strictly adhered to.
- Participants will be closely monitored for any signs and symptoms of COVID-19, including fever, dry cough, dyspnoea, sore throat, change in sense of smell or taste, and fatigue, throughout the study during the pandemic. Once clinical signs of infection are reported by participants, the investigator needs to determine whether samples can be collected, and safety data can be recorded on site. If not, adverse events (AEs) and

concomitant medications will be obtained via phone calls. The decision to continue with dosing the participant with the study intervention in the event of him/her showing symptoms of COVID-19 infection will be per investigator's discretion.

- Per site-specific and local guidance, it is suggested that participants who test positive for SARS-CoV-2 infection will be discontinued from the study and followed up until the outcome of the AE is established, per discussion with the sponsor.
- The probability of virus transmission will be controlled as much as possible by:
  - Advice for participant to adhere to local requirements for reduction of public exposure whilst ambulatory.
  - Confirmation of COVID-19 infection by laboratory assessments will be conducted based on availability (test capacity and turnaround time) of approved tests and on investigator's discretion.
  - Requesting that all participants are contacted by phone 1 day prior to every visit to assess COVID-19 symptoms and signs, and are asked not to attend the site in case of suspected reports. In addition, participants are asked about any contact with a person who has tested positive for SARS-CoV-2. If applicable, participants will be referred to the local healthcare system for further follow-up and treatment.
  - Physical distancing and person-to-person contact restrictions will be applied during site visits and in-house confinement.
  - Where physical distancing is not possible, personal protection equipment will be used by participants (surgical face mask, gloves) and staff (for example but not limited to masks, gloves, protectors, medical suits) if deemed appropriate by the Investigators and site staff and guided by local requirements.
  - Logistical improvements of the site and structural measures of the study site building will be implemented to further improve physical distancing.

J 3 Restrictions Related to COVID-19

During the COVID-19 pandemic, participants are advised to adhere to local requirements for reduction of the public SARS-CoV-2 exposure whilst ambulatory. If applicable, prior to Screening Visit 2, potential participants should be called to confirm they are not experiencing any COVID-19 symptoms and signs and are asked not to attend the site in case of suspected infection. If appropriate, participants will be referred to the local health care system. Physical distancing, appropriate face coverings (eg, face masks) and person-to-person contact restrictions will be applied and explained to participants whilst staying at the study site. Where physical distancing is not possible, participants will be asked to use surgical face masks and/or gloves if deemed appropriate by the investigator and site staff and guided by local requirements.

J 4 Data Quality Assurance

Site monitoring visits will be limited to a minimum required as deemed appropriate during COVID-19 pandemic, per local regulations.

In addition, where possible, other measures for carrying out protocol related activities, such as but not limited to home nursing and virtual outcome assessments, may be employed as required. If this is employed for this study a protocol amendment will be required.

J 5 Conclusion

Given the limited additional risks to the study population related to COVID-19 from study participation, beyond those they would experience in everyday life, the mitigations described are considered sufficient to ensure a favourable benefit-risk balance.

J 6 References

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency, March 2020, Updated on August 30, 2021.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency

Guidance on the Management of Clinical Trials during the COVID 19 (Coronavirus) pandemic, EMA, Version 5 (10/02/2022).
https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf

Appendix K Alcohol Use Disorder Identification Test (AUDIT)

Patient Reported Outcomes questionnaires under copyrights.

Patient Reported Outcomes questionnaires under copyrights.

Johnson et al 2013
Johnson JA, Lee A, Vinson D, Seale JP SO. Use of AUDIT-based measures to identify unhealthy alcohol use and alcohol dependence in primary care: a validation study Alcohol Clin Exp Res. 2013;37(1):253-9.

Appendix L Country-specific Requirements

As per the request of the Bundesinstitut für Arzneimittel und Medizinprodukt (BfArM), it was decided that it is not acceptable to have a legal representative to sign an Informed Consent Form for Germany. Consequently, all reference to legally authorised representatives were removed from the study protocol.

Appendix M Abbreviations

Abbreviation or special term	Explanation
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase/transaminase
ApoB	apolipoprotein B
APRI	AST to platelet ratio index
APTT	activated partial thromboplastin time
ASGR	asialoglycoprotein receptor
AST	aspartate aminotransferase/transaminase
ASO	antisense oligonucleotide
AUC	area under the curve
AV	Atrioventricular
BMI	body mass index
BP	blood pressure
CEA	clinical event adjudication
C_{max}	maximum serum concentration
COVID-19	Coronavirus disease 2019
CRN	Clinical Research Network
CRO	contract research organisation
CSP	clinical study protocol
CSR	clinical study report
CTIS	Clinical Trial Information System
CV	cardiovascular
DAE	AEs leading to discontinuation of study intervention
DBL	direct bilirubin
DILI	drug induced liver injury
DNA	deoxyribonucleic acid
iSMC	independent Safety Monitoring Committee
ECG	Electrocardiogram
EDV	Early discontinuation visit
EA	event adjudication
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate

Abbreviation or special term	Explanation
ELF	Enhanced Liver Fibrosis
EMA	European Medicines Agency
EU	European Union
EU CT	European Union Clinical Trial
FAS	full analysis set
FDA	United States Food and Drug Administration
FFPE	formalin-fixation and paraffin-embedding
FIB-4	Fibrosis-4
FiH	first in human
GalNAc	N-acetylgalactosamine
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GLDH	glutamate dehydrogenase
GLP	Good Laboratory Practice
GLP1 RA	glucagon-like peptide-1 receptor antagonist
GMAD	Global multiple ascending dose study
HbA1c	haemoglobin A1c
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDLc	high density lipoprotein cholesterol
HFF	hepatic fat fraction
HL	Hy's Law
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
hs-CRP	high-sensitivity C-reactive protein
IB	investigator's brochure
IATA	International Airline Transportation Associations
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IMP	investigational medicinal product
INR	international normalised ratio
IP	investigational product
IRB	Institutional Review Board

Abbreviation or special term	Explanation
IRT	interactive response technology
ISR	injection site reactions
IV	Intravenous
JMAD	Japan multiple ascending dose
LDLc	low density lipoprotein cholesterol
LFC	liver fat content
LLN	lower limit of normal
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MRE	magnetic resonance elastography
MRI-PDFF	magnetic resonance imaging-based protocol density fat fraction
mRNA	messenger ribonucleic acid
NAFLD	non-alcoholic fatty liver disease
NAS	NAFLD activity score
NASH	Non-alcoholic steatohepatitis
NSAID	non-steroidal anti-inflammatory drug
PCR	polymerase chain reaction
PD	Pharmacodynamics
PEF	Peak expiratory flow
PGIS	Patient Reported Outcome Measure for Patient Global Impression of Severity
PHL	Potential Hy's Law
PI	Principal investigator
PK	pharmacokinetic(s)
PNPLA3	patatin-like phospholipase domain-containing protein 3
PRO	patient reported outcome
PT	prothrombin time
QTcF	QT interval corrected by Fridericia's formula
RNA	ribonucleic acid
RTSM	randomisation and trial supply management
SAD	single ascending dose
SAE	serious adverse event
SAF	steatosis-activity-fibrosis
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous

Abbreviation or special term	Explanation
SF-36	Short Form 36-item
SGLT2i	sodium-glucose cotransporter-2 inhibitor
SNP	single nucleotide polymorphism
SRC	Safety review committee
SUSAR	suspected unexpected serious adverse reaction
SoA	schedule of activities
T2DM	type 2 diabetes mellitus
TBL	total bilirubin
ULN	upper limit of normal

Appendix N Protocol Version History

The Summary of Changes Table for the current revision is located directly before the Table of Contents.

CSP Version 4.0 [01-Jul-2024]

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

Overall Rationale for the Modification:

Current data supports removing the pre-dose platelet count visit (local lab, within 1 week of dosing to have a fresh platelet count) after Visit 11 and onwards, to reduce the participant visit burden in the study. After Visit 11 and onwards, the monthly ongoing safety surveillance and review of the independent Safety Monitoring Committee would be considered sufficient to detect any drop in platelet count. Actions in case of development of thrombocytopenia are described in Appendix F.

Summary of Changes:

List of Substantial Modifications

Overall Change	Description of Change	Brief Rationale	Impacted Section Number and Name
Removal of extra pre-dose platelet assessments after Visit 11.	Removal of requirement for extra platelet count sample after Visit 11.	Review of all available data shows no effect of AZD2693 on platelet count and supports current monitoring/mitigations to be sufficient without the pre-dose visits done within 1 week of dosing.	Table 1 (Schedule of Activities) 2.3.1.3 (Thrombocytopenia)
Removal of ECG assessments.	Removal of ECG assessments from study Visit 4, Visit 7, and Visit 20. Removal of ECG recordings at 60 to 120 minutes pre-dose and 4 hours post-dose at Visit 3 and Visit 13.	Results of concentration-QT modelling of AZD2693 SAD study showed no sign of QTcF prolongation up to the highest observed clinical exposure and no sign of drug induced effect on heart rate.	Table 1 (Schedule of Activities) 8.2.4 (Electrocardiograms)

List of Non-Substantial Modifications

Overall Change	Description of Change	Brief Rationale	Impacted Section Number and Name
Addition of EU CT number.	EU CT number added to the Title page.	Update per EU CT requirement.	Title page.
MRI-PDFF/MRE scan timepoints.	Removal of the word 'morning' for the fasting requirement and reference to 'for all measurements'. Addition of 'within a ± 2-hour window from the baseline scan.'	Clarification of requirements for MRI-PDFF/MRE scans.	Table 1 (Schedule of Activities) 8.1.3 (MRI-PDFF/MRE)
Removal of footnote.	Removal of footnote 'cc' from Schedule of Activities.	Information from footnote 'cc' already covered in footnote 'r'.	Table 1 (Schedule of Activities)
Removal of cholesteryl ester biomarker.	Removal of exploratory endpoint 'change from baseline in plasma cholesteryl ester 16:1/16:0 ratio' and reference to cholesteryl ester biomarker.	Review of the full dataset of the plasma cholesteryl ester 16:1/16:0 ratio from the SAD study and MAD study showed there is no treatment effect of AZD2693 on this biomarker.	Table 2 (Objectives and Endpoints) Table 8 (Pharmacodynamic Biomarkers) 9.4.2.2 (Secondary Endpoint[s])
Clarification of approved NASH treatments.	Clarification that there are no globally approved treatments for NASH and addition of approved therapies for the treatment of NASH to prohibited medications.	Approval of NASH treatment in the United States since the previous CSP version.	2.2 (Background) Table 5 (Prohibited Medications)
Clarification of reported ISRs.	Removal of 'transient' from description of reported ISRs.	To reflect that not all ISRs were resolved at the last study visit.	2.3.1.7 (Injection Site Reactions)
Addition of definition of total sexual abstinence.	Inclusion criterion regarding highly effective birth control reworded to define total sexual abstinence.	To align with the CSP template update.	5.1 (Inclusion Criteria)
Removal of reference to the Participant Interview Manual.	Removal of the following sentence 'Further details on the conduct of the Participant Qualitative interviews will be provided in the separate Participant Interview Manual' from the Participant Qualitative Interviews section.	The Participant Interview Manual is not available at study sites.	8.9 (Patient-Reported Outcome Questionnaires)

Overall Change	Description of Change	Brief Rationale	Impacted Section Number and Name
Clarification of analysis set definitions.	Addition of 'homozygous for the risk allele' to existing analysis sets, and addition of safety and full analysis sets for heterozygous participants.	To align with removal of heterozygous participants and SAP version 2.	9.3 (Populations for Analyses)
Clarification of primary analysis.	Addition of information regarding primary analysis.	To clarify the primary analysis.	9.4 (Statistical Analysis)
Addition of information regarding SUSARs.	Addition of information regarding the reporting of SUSARs and minor rewording of 'Regulatory Reporting Requirements for Serious Breaches of Protocol or GCP' section.	To align with CSP template update.	Appendix A 1 (Regulatory and Ethical Considerations)
Rewording of informed consent process	Rewording of sentence regarding re-consent if new information requires changes to the ICF and removal of reference to the Health Insurance Portability and Accountability Act.	To align with CSP template update.	Appendix A 3 (Informed Consent Process)
Addition of information regarding data protection.	Addition of information regarding data collection for business needs and pseudonymisation.	To align with CSP template update.	Appendix A 4 (Data Protection)
Addition of EU CT website.	Addition of 'https://euclinicaltrials.eu'	To align with CSP template update.	Appendix A 6 (Dissemination of Clinical Study Data)
Clarity on the definition of AEs	Removal of 'considered' from the definition of AE paragraph.	To align with CSP template update.	Appendix B 1 (Definition of Serious Adverse Events)
Addition of information regarding sample retention.	Addition of information regarding the length of sample retention and the returning of remaining samples to study site.	To align with CSP template update.	Appendix C 1 (Chain of Custody)
Addition of appendix	Addition of Appendix E 6 'Actions Required When Potential Hy's Law Criteria are met Before and After Starting Study Intervention' and renumbering of subsequent appendices to E 7 and E 8.	To align with CSP template update.	Appendix E 6 (Actions Required When Potential Hy's Law Criteria are met Before and After Starting Study Intervention)

Overall Change	Description of Change	Brief Rationale	Impacted Section Number and Name
General changes throughout CSP			
Minor revisions.	Minor editorial revisions.	To implement EU CTR requirements and correct minor typographical errors from the previous CSP version.	Throughout document

CSP Version 3.0 [04-Aug-2023]

This modification is considered to be substantial.

Overall Rationale for the Modification:

The Clinical Study Protocol (CSP), version 3.0, was updated to exclude the 50 mg exploratory heterozygous cohort. Heterozygous safety data had been reviewed during safety review committee (SRC) prior to the start of the Ph2b study, with no safety stopping criteria met and PK analysis in line with expectations. Efficacy data (liver fat content) is now available from the global multiple ascending dose study (GMAD) in the heterozygote participant cohort. The participants received 25 mg, 3 monthly doses and were followed for 16 weeks after the last dose. Review of the data from the ongoing study demonstrate a change in the benefit:risk ratio because there is not sufficient evidence of potential treatment benefit to support continued inclusion of this population in the D7830C00004 study.

Summary of Changes:

List of Substantial Modifications

Overall Change	Description of Change	Brief Rationale	Impacted Section Number and Name
Remove the exploratory heterozygote cohort	50 mg Heterozygous cohort has been removed from the study	Data from the ongoing GMAD study (D7830C00002) do not support the inclusion of the exploratory heterozygous cohort into the Ph2b 50 mg cohort.	1.1 (Synopsis) Figure 1 (Study Design) 2.1 (Study Rationale) 2.3.2 (Benefit Assessment) Table 2 (Objectives and Endpoints) 4.1 (Overall Design) 4.2 (Scientific Rationale for study design) 5.1 (Inclusion criteria) 9.2 (sample size determination) 9.4.2.3 (Exploratory endpoints) 9.4.3 (Safety)

List of Non-Substantial Modifications

Overall Change	Description of Change	Brief Rationale	Impacted Section Number and Name
Fasting conditions for safety samples at V1, V6, V8 and V23	Clarify that fasting is not required when collecting safety blood samples to measure only platelets, platelets and liver enzymes	Fasting is not a requirement when collecting certain safety samples	Table 1 (Schedule of Activities) 5.3.1 (Meals and Dietary Restrictions)
Fasting conditions for optional genetic samples	Clarify that fasting is not required when collecting blood samples for optional genetic analysis	Fasting status does not affect the genetic results and therefore is not mandatory	Table 1 (Schedule of Activities)
Fasting conditions for genotyping samples	Clarify that fasting is not required when collecting genotyping samples	Fasting status does not affect the genotype results and therefore is not mandatory	Table 1 (Schedule of Activities)
Include MRI-PDFF, MRE assessment as part of the EDV[a]	To include MRI-PDFF, MRE as part of the EDV activities only in participants who have received study intervention for at least 36 weeks assessment	GMAD data has shown MRI-PDFF changes as early as 12 weeks	Table 1 (Schedule of Activities)
Weight assessment	Clarification on Weight assessment	Weight is required in a gown, but some centers are not able to do this. It is acceptable for the sites to allow for 'light clothing	8.2.2 (Height, Weight, and Waist Circumference)
Temperature	Clarification on temperature measurement	Axillary temperature method is also allowed although not preferred	8.2.3 (vital signs)

Overall Change	Description of Change	Brief Rationale	Impacted Section Number and Name
Serum pregnancy test	Requirement for serum pregnancy test at the last follow-up visit and at the early discontinuation visit (EDV).	Requirements for pregnancy test where descripted in Section 5.1 of CSP v 2.0 but EDV time point was missed in the schedule of activities (SoA)	Table 1 (Schedule of Activities) Table 10 (Pregnancy and Hormone Testing)
Changes to the SoA	The study week timeline for Visit 2 has been changed from -8 to -7 Demography assessment at Visit 2 has been removed Pregnancy test at Visit 24 and EDV added MRI-PDFF, MRE assessments added at EDV visit along with a clarifying footnote Footnote "s" updated to provide more details on the sites at which MRI-PDFF/MRE assessments can be performed A note has been added after the table, clarifying which samples are allowed without fasting Footnote "d" updated to provide clarification on the screening visits Footnote "g" updated to clarify the timepoint of extra platelet sample collection Footnote "k" updated to clarify the timepoint of ALT values collection Footnote "bb" and "cc" added	To clarify the process	Table 1 (Schedule of Activities)
Number of subjects randomized	Number of subjects randomized has been updated from 232 to 180	Updated to only reflect the homozygous cohort as the exploratory heterozygous cohort has been removed	Section 1.1 (synopsis) Figure 1 (Study Design) Section 4.1 (Overall Design) Section 9.2 (Sample Size Determination)

Overall Change	Description of Change	Brief Rationale	Impacted Section Number and Name
Number of participants with low-level ALT increase	Number of participants with low-level increase in ALT updated from three participants to four participants	Provide updated information regarding low-level increase in ALT values in participants	Section 2.2 (Background) Section 2.3.1.5 (Liver toxicity-transaminase elevations)
Exclusion criteria clarified	Exclusion criteria #24 updated by adding virology Exclusion criteria #32 updated by adding alcohol dependence scoring	Exclusion criteria updated to provide clarification on HIV exclusionary criteria and add provide more clarity on alcohol dependence scoring	Section 5.2 (Exclusion criteria)
Blood collection volume updated	Amount of blood collected from patients during the study, updated from 900 to 960 mL	Amount of blood collected from patients updated to provide a more accurate estimate of blood volume.	Section 8 (Study assessments and procedures)
Updates to restricted medications	SGLT2i added to the list of restricted medications	To align with Inclusion Criterion #5 for participants treated with an SGLT2 inhibitor	Table 4 (Restricted medications)
AUDIT Questionnaire	Scoring of Audit questionnaire added	To provide details on scoring the questionnaire	Appendix K
New Section added	Implemented the mandatory updates required based on the recent protocol template	To align with the protocol template version 9.0	Section 6.2.1 (Dose preparation) Section 6.2.2 (Dose Administration)

Overall Change	Description of Change	Brief Rationale	Impacted Section Number and Name
Additional text added	Additional text which is the mandatory update required as per protocol template, added	To align with the protocol template version 9.0	Section 6.1 (Study interventions administered) Appendix A4 (Data Protection)
General changes throughout CSP			
Minor revisions	Minor editorial and document formatting revisions	To simplify or to clarify the process	Throughout Document

[a] To be done only at study sites with MRI-PDFF/MRE capability

CSP Version 2.0 [14-February-2023]

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

Overall Rationale for the Modification

The planned interim analysis of Liver Fat Content (LFC) and safety in the ongoing global MAD study ((D7830C00002), presumed NASH population, 25 and 50 mg monthly) has been completed. The result, combined with the overall project safety data and mRNA knock down predictions, were used to define the doses to be used in this Phase 2b study and update the Justification for Dose.

Data from the interim analysis suggest a low-level increase in mean absolute ALT. There are no confirmed platelet counts < 100 x 10^9/L or observations of mild or severe platelet count reductions. Safety monitoring and mitigations are updated in the CSP to reflect this data.

Summary of Changes:

List of Substantial Modifications

Overall Change	Description of Change	Brief Rationale	Impacted Section Number and Name
Additional ALT monitoring	ALT monitoring has been included every 2 weeks for 4 months (up to and including Week 16) and monthly thereafter	Data from ongoing studies support the additional ALT data collection and monitoring	Table 1 (Schedule of Activities) 8.2.5 (Clinical Safety Laboratory Assessments)

Overall Change	Description of Change	Brief Rationale	Impacted Section Number and Name
Less frequent platelet monitoring	Platelet monitoring has been reduced to every 2 weeks for 4 months (up to and including Week 16) and monthly thereafter. Clarification that platelet results should be available one week prior to dosing	Data from ongoing studies support the less frequent platelet monitoring	Table 1 (Schedule of Activities) 2.3.1.3 (Thrombocytopenia) 8.2.5 (Clinical Safety Laboratory Assessments)

List of Non-Substantial Modifications

Overall Change	Description of Change	Brief Rationale	Impacted Section Number and Name
The overall design has been defined	The study design has been revised to reflect the doses to be used for this study and the numbers of participants, and the potential options and outcomes have been removed	To provide up to date information from ongoing studies	1.1 (Synopsis) 4.1 (Overall Design) 1.3 (Schema) Figure 1 9.4.2.1 (Primary Endpoint) Table 3 (Investigational Products) 9.2 (Sample Size Determination)
Removal of interim analysis	The potential safety and efficacy evaluation at 24 weeks has been removed	To clarify the process	1.1 (Synopsis) 4.1 (Overall Design) 9.5 (Interim Analyses) Appendix A5 (Committees Structure)
DSMB naming change	References to DSMB (Data Safety Monitoring Board) changed to iSMC (independent Safety Monitoring Committee.)	To reflect the name change	1.1 (Synopsis) 9.6 (Data Monitoring Committee) Appendix A5 (Committees Structure)
NASH resolution definition has been clarified	The definition of resolution of NASH has been clarified	To clarify the process	(Synopsis, Objectives and Endpoints Table) Table 2 (Objectives and Endpoints)

Overall Change	Description of Change	Brief Rationale	Impacted Section Number and Name
Changes to the SoA	The visits at Week 18 and 22 have been removed 'Inclusion Criteria' changed to 'Eligibility Criteria' Drug accountability has been added onto the IP administration procedure Footnote 'f' has been clarified Footnote 'g' has been added to Week 20, 24 and 28 for IP administration and accountability Footnote 'g' has been added to Weeks 20, 24 and 28 for clinical safety labs Weight, waist and BMI measurement has been added from Week 28 to ensure measurements are captured monthly throughout the study Footnote 'q' clarified that a fresh biopsy sample can be taken, and an extension of the visit window Footnote 'j' has been clarified for liver enzymes measured Footnote 'l' has ALT included Footnote 'v' has been amended to include an extension to the visit window for Visits 13 and 21 Addition of GLDH measurement at baseline and Week 14, along with footnote 'y' An additional visit at Week 58 has been added for clinical safety lab samples, along with footnote 'z' Footnote 'aa' has been added The visit numbers from Week 20 onwards have been re-numbered	To clarify the process	Table 1 (Schedule of Activities)
Addition of GLDH measurement	Addition of GLDH measurement at baseline and Week 14	To provide additional information	Table 1 (Schedule of Activities) 8.2.5 (Clinical Safety Laboratory Assessments) Table 9 (Laboratory Safety Variables)
Clarification of HbA1c assessment visits	The table footnote has been corrected for the HbA1c assessment visits	To clarify the process	Table 9 (Laboratory Safety Variables)

Overall Change	Description of Change	Brief Rationale	Impacted Section Number and Name
Information from ongoing studies has been included	The information and data from ongoing studies has been updated throughout the document	To provide up to date information from ongoing studies	2.2 (Background) 2.3.1.3 (Thrombocytopenia) 2.3.1.7 (Injection Site Reactions) 4.3 (Justification for Dose)
Benefit/risk updates	The benefit/risk sections have been updated with data from ongoing studies The thrombocytopenia risk management has been updated with 'Participants with a confirmed platelet count outside the reference range' changed to 'Participants with a confirmed platelet count < LLN' Platelet count level monitoring updated to reflect the duration of monitoring and that values are required one week prior to dosing after month 4 Platelet count drop ranges have been clarified Clarification of liver transaminases to be continually measured	To provide up to date information from ongoing studies	2.2 (Background) 2.3.1.3 (Thrombocytopenia) 2.3.1.5 (Liver Toxicity – Transaminase Elevations) 2.3.1.7 (Injection Site Reactions) 2.3.3 (Overall Benefit: Risk Conclusion)
Primary Estimand clarification	The Primary Estimand section has been included The strategy for the primary estimands of histology endpoints and intercurrent events for liver outcomes has been clarified	To clarify the process	3 (Objectives, Endpoints and Estimands) 9.4.2 (Efficacy)
Stratification clarification	Clarification that participants will be stratified by presence/absence of T2DM and by fibrosis stage	To clarify the process	6.3 (Measures to minimise bias) 9.2 (Sample Size Determination)
Addition of exploratory objective	An exploratory objective to explore treatment effects on plasma derived cell free DNA has been included	To provide additional information	Table 2 (Objectives and Endpoints) Table 1 (Schedule of Activities) 8.1.2 (Biomarkers) 8.6.2 (Collection of mandatory samples for bioanalysis)
Inclusion criteria clarified	COVID-19 status has been clarified	To clarify the process	5.1 (Inclusion Criteria)

Overall Change	Description of Change	Brief Rationale	Impacted Section Number and Name
Exclusion criteria clarified	HCV RNA reflex test criteria added Significant COVID-19 illness criteria added Confirmed platelet count criteria at screening changed from 'outside the normal range' to '<LLN' Addition of footnote to define the term 'confirmed'	To clarify the process	5.2 (Exclusion Criteria)
Clarification of Discontinuation of Study Intervention	Any case of Potential Hy's Law' has been removed as this is covered by another point Addition of text for participants that discontinue treatment S-retinol discontinuation criteria has been removed	To clarify the process	7.1 (Discontinuation of Study Intervention)
S-retinol discontinuation criteria removed	The discontinuation criteria for S-retinol has been removed based on the latest information from ongoing studies	To clarify the process	2.3.1.1 (Inhibition of *PNPLA3*) 7.1 (Discontinuation of Study Intervention)
Paternal exposure section removed	The paternal exposure section has been removed to provide consistency throughout the document on pregnancy based on the latest information from ongoing studies	To clarify the process	8.3.9.2 (Paternal Exposure)
Blood volume revised	The maximum amount of blood to be collected has been revised	To clarify the process	8 (Study Assessment and Procedures)
Analysis sets have been clarified	ADA set has been included FAS has been amended to include participants who received at least one dose	To clarify the process	Table 12 (Populations for Analysis) 9.4.2 (Efficacy)
DILI Algorithm simplified	Table 6 has been simplified, and the tables merged into one Figures 2 and 3, flow charts reflecting the algorithm have been added to aid decision making	To clarify the process	6.6.1 (Monitoring and Management Plan for Possible DILI), Table 6 (DILI Algorithm)
Administration of study intervention footnote clarified	The administration of study intervention process has been clarified	To clarify the process	Table 3 (Investigational Products)
Screen failure clarification	Clarification of allowed ALT rescreening Clarification of when rescreening is not allowed has been clarified	To clarify the process	5.4 (Screen Failures)

Overall Change	Description of Change	Brief Rationale	Impacted Section Number and Name
Addition of ApoB measurement	Addition of ApoB biomarker measurement	To provide additional information	Table 2 (Objectives and Endpoints) Table 8 (PD Biomarkers) 9.4.2.3 (Tertiary/Exploratory Endpoints)
Inclusion of temporary discontinuation section	A section on temporary discontinuation of study intervention has been added		7.1.1 (Temporary Discontinuation of Study Intervention)
Liver Volume measurement procedure clarification	The procedure for measuring liver volume has been clarified	To clarify the process	8.1.3 (MRI-PDFF/MRE)
Clarification of documentation for ISRs	The process of documenting ISRs has been clarified	To clarify the process	8.2.6 (Other Safety Assessments)
Liver biopsy clarification	Clarification that a new biopsy sample should be taken if the historical one is of poor quality	To clarify the process	8.5.4 (Liver Biopsy)
ECG recording window extended	An extension to the ECG recording window has been included to allow sites sufficient time	To clarify the process	8.2.4 (Electrocardiograms)
Removal of buccal swab requirement	Removal of reference to buccal swab samples which was previously included in error	To clarify the process	Appendix D (Optional Genomics Initiative Sample)
Text added to align with the latest template version	Text has been added to reflect current AZ processes and to align with the current template version	To align with the latest template version	4.4 (End of Study Definition) 8.4 (Overdose) Appendix A6 (Dissemination of Clinical Study Data) Appendix A7 (Data Quality Assurance) Appendix B4 (Medication Error, Drug Abuse, and Drug Misuse)
Inclusion of country specific appendix	Addition of new appendix to cover German HA requirements	To provide country-specific information	Appendix L (Country-specific Requirements)
Inclusion of AUDIT questionnaire appendix	Addition of the AUDIT questionnaire	To clarify the process	Appendix K (AUDIT) 5.2 (Exclusion Criteria)

Overall Change	Description of Change	Brief Rationale	Impacted Section Number and Name
Minor revisions	Minor editorial and document formatting revisions	To clarify the process	Throughout Document
Visits have been re-numbered	Due to the removal of visits at Weeks 18 and 22, the visit numbers have been revised throughout the document	To clarify the process	Throughout Document

11 REFERENCES

Angulo 2007
Angulo P. GI epidemiology: nonalcoholic fatty liver disease. Aliment Pharmacol Ther. 2007;25(8):883-9. doi:10.1111/j.1365-2036.2007.03246.x.

Angulo et al 2015
Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, et al. Liver Fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology. 2015;149(2):389-97.e10. doi:10.1053/j.gastro.2015.04.043.

Basantani et al 2011
Basantani MK, Sitnick MT, Cai L, Brenner DS, Gardner NP, Li JZ, et al. Pnpla3/Adiponutrin deficiency in mice does not contribute to fatty liver disease or metabolic syndrome. J Lipid Res. 2011;52(2):318-29. doi:10.1194/jlr.M011205.

Bellentani 2017
Bellentani S. The epidemiology of non-alcoholic fatty liver disease. Liver Int. 2017;37 Suppl 1:81-4. doi:10.1111/liv.13299.

Bellentani et al 2010
Bellentani S, Scaglioni F, Marino M, Bedogni G. Epidemiology of nonalcoholic fatty liver disease. Dig Dis. 2010;28(1):155-61. doi:10.1159/000282080.

Burdick et al 2014
Burdick AD, Sciabola S, Mantena SR, Hollingshead BD, Stanton R, Warneke JA, et al. Sequence motifs associated with hepatotoxicity of locked nucleic acid--modified antisense oligonucleotides. Nucleic Acids Res. 2014;42(8):4882-91. doi:10.1093/nar/gku142.

Burel et al 2013
Burel SA, Han SR, Lee HS, Norris DA, Lee BS, Machemer T, et al. Preclinical evaluation of the toxicological effects of a novel constrained ethyl modified antisense compound targeting signal transducer and activator of transcription 3 in mice and cynomolgus monkeys. Nucleic Acid Ther. 2013;23(3):213-27. doi:10.1089/nat.2013.0422.

Burel et al 2016
Burel SA, Hart CE, Cauntay P, Hsiao J, Machemer T, Katz M, et al. Hepatotoxicity of high affinity gapmer antisense oligonucleotides is mediated by RNase H1 dependent promiscuous reduction of very long pre-mRNA transcripts. Nucleic Acids Res. 2016;44(5):2093-109. doi:10.1093/nar/gkv1210.

Chalasani et al 2018
Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67(1):328-57. doi:10.1002/hep.29367.

Cholankeril et al 2017
Cholankeril G, Patel R, Khurana S, Satapathy SK. Hepatocellular carcinoma in non-alcoholic steatohepatitis: Current knowledge and implications for management. World J Hepatol. 2017;9(11):533-43. doi:10.4254/wjh.v9.i11.533.

Crooke et al 2016
Crooke ST, Baker BF, Kwoh TJ, Cheng W, Schulz DJ, Xia S, et al. Integrated Safety Assessment of 2'-O-Methoxyethyl Chimeric Antisense Oligonucleotides in NonHuman Primates and Healthy Human Volunteers. Mol Ther. 2016;24(10):1771-82. doi:10.1038/mt.2016.136.

Crooke et al 2017
Crooke ST, Baker BF, Witztum JL, Kwoh TJ, Pham NC, Salgado N, et al. The effects of 2′-O-methoxyethyl containing antisense oligonucleotides on platelets in human clinical trials. Nucleic Acid Ther. 2017;27(3):121-9. doi:10.1089/nat.2016.0650.

Crooke et al 2018
Crooke ST, Witztum JL, Bennett CF, Baker BF. RNA-Targeted Therapeutics. Cell Metab. 2018;27(4):714-39. doi: 10.1016/j.cmet.2018.03.004.

Doward et al 2021
Doward LC, Balp MM, Twiss J, Slota C, Cryer D, Brass CA, et al. Development of a patient-reported outcome measure for non-alcoholic steatohepatitis (NASH-CHECK): results of a qualitative study. Patient. 2021;14(5):533-43. doi:10.1007/s40271-020-00485-w.

Engelhardt et al 2015
Engelhardt JA, Fant P, Guionaud S, Henry SP, Leach MW, Louden C, et al. Scientific and Regulatory Policy Committee Points-to-consider Paper: Drug-induced vascular injury associated with non-small molecule therapeutics in preclinical development, Part 2: Antisense oligonucleotides. Toxicol Pathol. 2015;43(7):935-44. doi:10.1177/0192623315570341.

Foundation for the National Institutes of Health 2019
Foundation for the National Institutes of Health and Critical Path Institute. User's guide: kidney safety composite measure biomarker for use in clinical development, version 1.1. Published May 15, 2019. https://fnih.org/sites/default/files/pdf/KSP-CompositeCOU-UserGuide-V1.1_20190515.pdf

Frazier 2015
Frazier KS. Antisense oligonucleotide therapies: the promise and the challenges from a toxicologic pathologist's perspective. Toxicol Pathol. 2015;43(1):78-89. doi:10.1177/0192623314551840.

Grimaudo et al 2020
Grimaudo S, Pipitone RM, Pennisi G, Celsa C, Camma C, Di Marco V, et al. Association between PNPLA3 rs738409 C>G variant and liver-related outcomes in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2020;18(4):935-44.e3. doi:10.1016/j.cgh.2019.08.011.

Hagedorn et al 2013
Hagedorn PH, Yakimov V, Ottosen S, Kammler S, Nielsen NF, Høg AM, et al. Hepatotoxic potential of therapeutic oligonucleotides can be predicted from their sequence and modification pattern. Nucleic Acid Ther. 2013;23(5):302-10. doi:10.1089/nat.2013.0436.

Henry et al 1997
Henry SP, Novotny W, Leeds J, Auletta C, Kornbrust DJ. Inhibition of coagulation by a phosphorothioate oligonucleotide. Antisense Nucleic Acid Drug Dev. 1997;7(5):503-10. doi:10.1089/oli.1.1997.7.503.

Hildebrandt-Eriksen et al 2012
Hildebrandt-Eriksen ES, Aarup V, Persson R, Hansen HF, Munk ME, Ørum H. A locked nucleic acid oligonucleotide targeting microRNA 122 is well-tolerated in cynomolgus monkeys. Nucleic Acid Ther. 2012;22(3):152-61. doi:10.1089/nat.2011.0332.

Hung et al 2013
Hung G, Xiao X, Peralta R, Bhattacharjee G, Murray S, Norris D, et al. Characterization of target mRNA reduction through in situ RNA hybridization in multiple organ systems following systemic antisense treatment in animals. Nucleic Acid Ther. 2013;23(6):369-78. doi:10.1089/nat.2013.0443.

Iqbal et al 2019
Iqbal U, Perumpail BJ, Akhtar D, Kim D, Ahmed A. The epidemiology, risk profiling and diagnostic challenges of nonalcoholic fatty liver disease. Medicines (Basel). 2019;6(1):41. doi:10.3390/medicines6010041.

Johnson et al 2013
Johnson JA, Lee A, Vinson D, Seale JP SO. Use of AUDIT-based measures to identify unhealthy alcohol use and alcohol dependence in primary care: a validation study Alcohol Clin Exp Res. 2013;37(1):253-9.

Kallwitz et al 2019
Kallwitz ER, Tayo BO, Kuniholm MH, Cai J, Daviglus M, Cooper RS, et al. American ancestry is a risk factor for suspected nonalcoholic fatty liver disease in Hispanic/Latino adults. Clin Gastroenterol Hepatol. 2019;17(11):2301-9. doi:10.1016/j.cgh.2019.02.007.

Kato et al 2012
Kato SI, Nagata K, Takeuchi K. Cell tropism and pathogenesis of measles virus in monkeys. Front Microbiol. 2012;3:14. doi:10.3389/fmicb.2012.00014

Kleiner et al 2014
Kleiner DE, Chalasani NP, Lee WM, Fontana RJ, Bonkovsky HL, Watkins PB, et al. Hepatic histological findings in suspected drug-induced liver injury: systematic evaluation and clinical associations. Hepatology. 2014;59(2):661-70. doi:10.1002/hep.26709.

Linden et al 2019
Lindén D, Ahnmark A, Pingitore P, Ciociola E, Ahlstedt I, Andréasson A-C, et al. Pnpla3 silencing with antisense oligonucleotides ameliorates nonalcoholic steatohepatitis and fibrosis in Pnpla3 I148M knock-in mice. Mol Metab. 2019;22:49-61. doi:10.1016/j.molmet.2019.01.013.

Maruish 2011
Maruish ME (Ed.). User's manual for the SF-36v2 Health Survey. 3rd ed. QualityMetric Incorporated; 2011.

Mishra and Younossi 2012
Mishra A, Younossi ZM. Epidemiology and natural history of non-alcoholic fatty liver disease. J Clin Exp Hepatol. 2012;2(2):135-44. doi:10.1016/S0973-6883(12)60102-9.

Nalbantoglu and Brunt 2014
Nalbantoglu I, Brunt EM. Role of liver biopsy in nonalcoholic fatty liver disease. World J Gastroenterol. 2014;20(27):9026-37. doi:10.3748/wjg.v20.i27.9026

Pais et al 2016
Pais R, Barritt AS, Calmus Y, Scatton O, Runge T, Lebray P, et al. NAFLD and liver transplantation: Current burden and expected challenges. J Hepatol. 2016;65(6):1245-57. doi:10.1016/j.jhep.2016.07.033.

Pingitore and Romeo 2019
Pingitore P, Romeo S. The role of PNPLA3 in health and disease. Biochim Biophys Acta Mol Cell Biol Lipids. 2019;1864(6):900-6. doi:10.1016/j.bbalip.2018.06.018.

Pirazzi et al 2014
Pirazzi C, Valenti L, Motta BM, Pingitore P, Hedfalk K, Mancina RM, et al. PNPLA3 has retinyl-palmitate lipase activity in human hepatic stellate cells. Hum Mol Genet. 2014;23(15):4077-85. doi:10.1093/hmg/ddu121.

Regev et al 2019
Regev A, Palmer M, Avigan MI, Dimick-Santos L, Treem WR, Marcinak JF, et al. Consensus: guidelines: best practices for detection, assessment and management of suspected acute drug-induced liver injury during clinical trials in patients with nonalcoholic steatohepatitis. Aliment Pharmacol Ther. 2019;49(6):702-13. doi:10.1111/apt.15153.

Rich et al 2018
Rich NE, Oji S, Mufti AR, Browning JD, Parikh ND, Odewole M, et al. Racial and ethnic disparities in nonalcoholic fatty liver disease prevalence, severity, and outcomes in the United States: A systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2018;16(2):198-210.e2. doi:10.1016/j.cgh.2017.09.041.

Romeo et al 2008
Romeo S, Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nat Genet. 2008;40(12):1461-5. doi:10.1038/ng.257.

Salameh et al 2016
Salameh H, Hanayneh MA, Masadeh M, Naseemuddin M, Matin T, Erwin A, et al. PNPLA3 as a genetic determinant of risk for and severity of non-alcoholic fatty liver disease spectrum. J Clin Transl Hepatol. 2016;4(3):175-91. doi:10.14218/JCTH.2016.00009.

Santos et al 2015
Santos RD, Duell PB, East C, Guyton JR, Moriarty PM, Chin W, et al. Long term efficacy and safety of mipomersen in patients with familial hypercholesterolemia: 2-year interim results of an open label extension. Eur Heart J. 2015;36(9):566-75. doi:10.1093/eurheartj/eht549.

Sewell et al 2002
Sewell KL, Geary RS, Baker BF, Glover JM, Mant TG, Yu RZ, et al. Phase I trial of ISIS 104838, a 2'-methoxyethyl modified antisense oligonucleotide targeting tumor necrosis factor-alpha. J Pharmacol Exp Ther. 2002;303(3):1334-43. doi:10.1124/jpet.102.036749.

Unalp-Arida and Ruhl 2020
Unalp-Arida A, Ruhl CE. Patatin-like phospholipase domain-containing protein 3 I148M and liver fat and fibrosis scores predict liver disease mortality in the U.S. population. Hepatology. 2020;71(3):820-34. doi:10.1002/hep.31032.

van Meer et al 2017
van Meer L, van Dongen M, Moerland M, de Kam M, Cohen A, Burggraaf J. Novel SGLT2 inhibitor: first-in-man studies of antisense compound is associated with unexpected renal effects. Pharmacol Res Perspect. 2017;5(1):e00292. doi:10.1002/prp2.292.

van Poelgeest et al 2013
van Poelgeest EP, Swart RM, Betjes MG, Moerland M, Weening JJ, Tessier Y, et al. Acute kidney injury during therapy with an antisense oligonucleotide directed against PCSK9. Am J Kidney Dis. 2013;62(4):796-800. doi:10.1053/j.ajkd.2013.02.359.

van Poelgeest et al 2015
van Poelgeest EP, Hodges MR, Moerland M, Tessier Y, Levin AA, Persson R, et al. Antisense-mediated reduction of proprotein convertase subtilisin/kexin type 9 (PCSK9): a first-in-human randomized, placebo-controlled trial. Br J Clin Pharmacol. 2015;80(6):1350-61. doi:10.1111/bcp.12738.

Walker et al 2020
Walker RW, Belbin GM, Sorokin EP, van Vleck T, Wojcik GL, Moscati A, et al. A common variant in PNPLA3 is associated with age at diagnosis of NAFLD in patients from a multi-ethnic biobank. J Hepatol. 2020;72(6):1070-81. doi:10.1016/j.jhep.2020.01.029.

Wijarnpreecha et al 2021
Wijarnpreecha K, Scribani M, Raymond P, Harnois DM, Keaveny AP, Ahmed A, et al. PNPLA3 gene polymorphism and liver- and extrahepatic cancer-related mortality in the United States. Clin Gastroenterol Hepatol. 2021;19(5):1064-6. doi:10.1016/j.cgh.2020.04.058.

Wong et al 2014
Wong RJ, Cheung R, Ahmed A. Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. Hepatology. 2014;59(6):2188-95. doi:10.1002/hep.26986.

Xu et al 2015
Xu R, Tao A, Zhang S, Deng Y, Chen G. Association between patatin-like phospholipase domain containing 3 gene (PNPLA3) polymorphisms and nonalcoholic fatty liver disease: a HuGE review and meta-analysis. Sci Rep. 2015;5:9284. doi:10.1038/srep09284.

Younossi et al 2016
Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73-84. doi:10.1002/hep.28431.

Younossi et al 2018
Younossi ZM, Loomba R, Rinella ME, Bugianesi E, Marchesini G, Neuschwander-Tetri BA, et al. Current and future therapeutic regimens for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Hepatology. 2018;68(1):361-71. doi:10.1002/hep.29724.

Signature Page for VV-RIM-02749211 System v8.0
D7830C00004 Clinical Study Protocol version 5

Approve: Document Level Task Verdict: Approved	PPD Content Approval 08-Apr-2025 15:17:19 GMT+0000

Approve: Document Level Task Verdict: Approved	PPD Content Approval 08-Apr-2025 18:45:22 GMT+0000

Approve: Document Level Task Verdict: Approved	PPD Content Approval 09-Apr-2025 07:36:34 GMT+0000

Signature Page for VV-RIM-02749211 System v8.0
D7830C00004 Clinical Study Protocol version 5