A PHASE 2, RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, PLACEBO-CONTROLLED, DOSE-RANGING, DOSE-FINDING, PARALLEL GROUP STUDY TO ASSESS EFFICACY AND SAFETY OF PF-06865571 (DGAT2I) ALONE AND WHEN COADMINISTERED WITH PF-05221304 (ACCI) IN ADULT PARTICIPANTS WITH BIOPSY-CONFIRMED NONALCOHOLIC STEATOHEPATITIS AND FIBROSIS STAGE 2 OR 3

Study Intervention Number:	PF-06865571 (DGAT2i); PF-05221304 (ACCi)
Study Intervention Name:	N/A
US IND Number:	133322 (DGAT2i)
EudraCT Number:	2019-004775-39
ClinicalTrials.gov ID:	NCT04321031
Protocol Number:	C2541013
Phase:	2

Short Title: Metabolic Interventions to Resolve NASH with Fibrosis (MIRNA)

Protocol Amendment Summary of Changes Table

Document	Version Date
Amendment 1	30 August 2021
Original protocol	22 January 2020

This amendment incorporates all revisions to date, including revisions made at the request of country health authorities and IRBs/ECs and any protocol administrative clarification letters.

Protocol Amendment Summary of Changes Table

Amendment 1 30 August 2021

Overall Rationale for the Amendment: This substantial amendment is a result of a strategic decision to reprioritize the number of scientific questions being addressed by this study after accounting for the totality of data generated across multiple studies. Via this protocol amendment, this study will focus on an evaluation of dose-ranging, dosing-finding, efficacy, and safety, of BID dosing regimens of DGAT2i alone, or when coadministered with ACCi.

This amendment was deemed necessary in light of the operational challenges during the ongoing, global COVID-19 pandemic. This change is not prompted by emerging safety data in this or other ongoing studies in the program. Data from all randomized participants will be used to ascertain efficacy and safety of DGAT2i alone, and DGAT2i + ACCi.

Section #, Title	Description of Change	Brief Rationale
Key Changes		

Synopsis; Section 2.3.2, Benefit Assessment; Section 4.3, Justification of Dose; Section 6.1, Study Intervention(s) Administered – Table 3; Section 6.3.1, Allocation of Study Intervention; Section 9.2, Sample Size Determination	• Evaluation of 2 arms with administration of DGAT2i alone (150 mg QD and 300 mg QD) is no longer being pursued
	  • Those previously randomized to these 2 arms will be switched in a blinded manner to receive the corresponding BID regimen that maintains the same total daily dose
	• Ratio of those on investigational agent(s) decreased slightly –
	  • Original protocol was 89% (8 of 9)
	  • Protocol Amendment 1 will be 86% (6 of 7)
		Strategic decision to reprioritize the number of scientific questions being addressed by this study

Section 9.1, Estimands and Statistical Hypotheses; Section 9.2, Sample Size	• Clarifications offered for each estimand and planned analyses across the treatment arms	Outline intent to use data from those randomized to the 2 arms not being pursued towards the overall assessment of efficacy and safety

Section #, Title	Description of Change	Brief Rationale
Determination; Section 9.3, Analysis Sets; Section 9.4, Statistical Analyses		
Section 9.5, Interim Analysis	Number randomized to trigger 1st safety review by E-DMC retained but proportion updated (from approximately 25%, ~112 participants to 33%, ~115 participants)	Ensure timely E-DMC review and oversight of participants safety
Section 1.2, Schema; SoA-Table A1, A2; Section CCI Section 4.1, Overall Design; Section 4.2, Scientific Rationale for Study Design; Section 4.2.3, Participant Input Into Study Design; Section 6.5, Concomitant Therapy	Update to capture circumstances that permit Run-In/Visit 3 to be conducted as a telephone contact vs on-site visit ***while*** maintaining a stabilization period of ***at least 4-weeks*** before Baseline/Visit 4 – as outlined in study-level PACL issued June 2021	• Permits time between conduct of SCR2 biopsy and when SCR2 results are reported by sponsor-identified central laboratory to be used as part of the protocol-mandated minimum 4 week of stabilization period prior to Baseline/Visit 4 • The revisions here will minimize out-of-window randomization (ie, minor protocol deviations of PreQ to Day 1 in greater than 16 weeks) uniquely attributed to delays in reporting of SCR2 biopsy results by the sponsor-identified central laboratory and offers ability to manage this potential delay while retaining the scientific integrity of the study design
Section 4.2, Scientific Rationale for Study Design; Section 5.1, Inclusion criteria (#3, #4)	Beyond FAST™ score, permit use of ***only*** FibroScan® derived parameters, CAP™ and VCTE™	Expansion beyond use of FAST™ score to noninvasively identify population with presumed NASH **but** adding the vigor of requiring the ***same criteria*** to be met at both PreQ and SCR1
Section 4.2, Scientific Rationale for Study Design; Section 5.1, Inclusion criteria (#6)	Revision to upper limit of BMI from 40 kg/m^2 to 45 kg/m^2	• Target patient population is overweight and obese • Integrity of conduct retained with requirement for ***evaluable*** FibroScan® data and permitting conduct of computed tomography guided (in addition to ultrasound guided) percutaneous liver biopsy
Section 5.5, Screen Failures	Provisions added which permit re-screening of those who were excluded under Original Protocol but would qualify against revised eligibility criterion #3, #4, and/or #6	Those deemed eligible per Protocol Amendment 1 offered an opportunity to join this study
Administrative changes		
Objectives, Estimands, Endpoints	Clarifications added to more accurately reflect the estimand definition and planned analysis	Revisions to aide clarity/ transparency
Section 2.2.2, Clinical Overview	Updates made to reflect DGAT2i IB dated February 2021	Align content to most recent SRSD

Section #, Title	Description of Change	Brief Rationale
Section 5.2, Exclusion criteria (#13); Section 8.2, Safety Assessment	Guidance offered regarding COVID-19 vaccination, and management of those who test positive and/or are symptomatic – reflected in study-level PACL issued January 2021	Additions made given ongoing COVID-19 pandemic into this amendment
Section 6.5, Concomitant Therapy	Additional examples of agents permitted, prohibited – added	Incorporate clarifying queries regarding protocol language received from sites since initiation of study ensuring uniform execution of study across all regions
Section 8.1.2.2, Assessment of Liver Fat using MRI-PDFF (Imaging Substudy)	Clarification added outlining the 1 region included in Imaging Substudy; all other regions are excluded	Offer transparency to Health Authorities, IRBs, ECs regarding the limited scope of this substudy
Section 8, Study Assessments and Procedures	Blood volume collected offered for the full range being collected across all 11 countries in this study	Content consistently capturing volume in country- and site- level ICDs
Appendix 10, Guidance to Investigators	Collection of blood to permit assessment of FPG±HbA1C added, in participants in whom metformin dose is adjusted at Run-In/Visit 3	Need for additional vigilance with assessment of glycemia post randomization reinforced
Section 8.1.2.2, Assessment of Liver Fat using MRI-PDFF (Imaging Substudy); Section 9.4, Statistical Analyses	Clarifications added to the descriptions of analyses as well as additional detail added regarding exploratory MRI-derived endpoints ([redacted])	Align with the details already included in the SAP
Appendix 10.4.1, Male Participant Reproductive Inclusion Criteria	Country-Specific ([redacted] only) requirement for contraception in males reflected in PACL issued April 2020	Additions made according to requirements from the Regulatory authority in [redacted]
Section 6.5.4, other acceptable concomitant medications; Appendix [redacted] inhibitors and inducers	Country-Specific ([redacted] only) requirement for concomitant use of herbal preparations offered via PACL issued February 2021	In response to the uniquely disproportionate use of herbal preparations, in the population being enrolled in this study, guidance offered to Investigators
Appendix 2, Clinical Laboratory Tests	Country-Specific ([redacted] only) requirements addressed; PACL issued January 2021 incorporated	Inability to export samples from [redacted], for analysis of 3 unique analytes (ProC3, ProC6, direct VLDL) necessitated removal of blood collections for these parameters in all participants consented and randomized in [redacted] in this study
Appendix 5, Genetics	Country-Specific ([redacted] only) requirements addressed; PACL issued May-2020 and August 2020 incorporated	Scope of exploratory genetic analyses limited, per local requirements
Throughout document	Clarifications offered to aide in a common understanding of the protocol across all sites and all countries	Incorporate clarifying queries regarding protocol language received from sites since initiation of study ensuring uniform execution of study

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: **M**etabolic **I**nterventions to **R**esolve **NA**SH with Fibrosis (MIRNA)

Rationale: The current study aims to evaluate two, orally administered, investigational agents - PF-06865571, a small molecule that selectively inhibits DGAT2 and the coadministration of PF-06865571 with PF-05221304, a selective, reversible, inhibitor of ACC, for the treatment of NASH with liver fibrosis. This is the first clinical study specifically designed to evaluate the effect of a range of doses of DGAT2i alone, administered BID, and DGAT2i + ACCi administered BID, on resolution of NASH or improvement in liver fibrosis, as assessed histologically (via liver biopsy). Additionally, exploratory assessment of non-invasive imaging-based and blood-based collections are planned to enable potential identification of non-invasive markers of disease and/or treatment response – in the target adult population.

Objectives, Estimands, and Endpoints: The primary, secondary, and key tertiary endpoints of focus in this study include –

Objectives	Estimands	Endpoints
Primary:		
To evaluate the effect of a range of DGAT2i doses administered alone, and coadministration of DGAT2i + ACCi, compared to placebo, and the coadministration of DGAT2i + ACCi relative to DGAT2i alone, ***in participants with biopsy confirmed NASH and fibrosis, on resolution of NASH without worsening of fibrosis or improvement in fibrosis by ≥1 stage without worsening of NASH, or both***	Using a composite estimand strategy in participants with biopsy-confirmed NASH and fibrosis, estimate the treatment effect of DGAT2i doses administered alone and coadministration of DGAT2i + ACCi relative to placebo, and coadministration of DGAT2i + ACCi, relative to DGAT2i alone, in terms of the proportion of 'clinical responders', defined as participants achieving centrally adjudicated: resolution of NASH without worsening of fibrosis or improvement in fibrosis by ≥1 stage without worsening of NASH, or both, at Week 48 and treating all cases of withdrawal from treatment for lack of efficacy or toleration as non-responders • All treatment effect contrasts will be obtained through fitting the Bayesian dose-response and/or exposure-response models with a logit transformation, or logistic regression models	Proportion of participants achieving resolution of NASH without worsening of fibrosis ***or*** improvement in fibrosis by ≥1 stage without worsening of NASH ***or*** both, based on assessment by sponsor-identified central pathologist(s), at Week 48
Secondary:		
To evaluate the effect of a range of DGAT2i doses administered alone, and coadministration of DGAT2i + ACCi, compared to placebo, and the coadministration of DGAT2i + ACCi relative to DGAT2i alone, on ***liver fat***	Using a hypothetical estimand strategy, in participants with biopsy-confirmed NASH and fibrosis, estimate the treatment effect of DGAT2i doses administered alone and coadministration of DGAT2i + ACCi relative to placebo, and coadministration of DGAT2i + ACCi, relative to DGAT2i alone, in terms of the population level average percentage change from baseline in liver fat (assessed via MRI-PDFF) at Week 48, assuming all participants had remained in the trial and received treatment as planned without withdrawal up to 48 Weeks. Endpoint data	Percent change in liver fat (assessed via MRI-PDFF in substudy population), at Week 48

Objectives	Estimands	Endpoints
	collected after treatment withdrawal will be censored. • All treatment effect contrasts will be obtained through fitting the Bayesian dose-response and/or exposure-response models, or ANCOVA models	
To evaluate the effect of a range of DGAT2i doses administered alone, and coadministration of DGAT2i + ACCi, compared to placebo, and the coadministration of DGAT2i + ACCi relative to DGAT2i alone, ***in participants achieving improvement in different responder definitions***	Using a composite estimand strategy in participants with biopsy-confirmed NASH and fibrosis, estimate the treatment effect of DGAT2i doses administered alone and coadministration of DGAT2i + ACCi relative to placebo, and coadministration of DGAT2i + ACCi, relative to DGAT2i alone, in terms of the proportion of 'clinical responders', defined as participants achieving centrally adjudicated resolution of NASH without worsening of fibrosis at Week 48 and treating all cases of withdrawal from treatment for lack of efficacy or toleration as non-responders • All treatment effect contrasts will be obtained through fitting the Bayesian dose-response and/or exposure-response models with a logit transformation, or logistic regression models • Similar estimands will be assessed for: • Improvement in fibrosis by ≥1 stage, without worsening of NASH • Improvement in fibrosis by ≥2 stages, without worsening of NASH • Improvement of ≥2 points in Total NAFLD Activity Score (NAS)	Proportion of participants achieving improvement in different responder definitions based on assessment by sponsor-identified central pathologist(s) at Week 48 – • Resolution of NASH, without worsening of fibrosis • Improvement in fibrosis by ≥1 stage, without worsening of NASH • Improvement in fibrosis by ≥2 stages, without worsening of NASH • Improvement of ≥2 points in Total NAS
To assess the ***safety and tolerability*** with a range of DGAT2i doses administered alone, and coadministration of DGAT2i + ACCi, compared to placebo, and the coadministration of DGAT2i + ACCi relative to DGAT2i alone		Assessment of TEAEs, safety-related clinical laboratory tests, vital signs, and 12-lead ECGs, over time up to Week 48
Tertiary/Exploratory:		
To evaluate the effect of a range of DGAT2i doses administered alone, and coadministration of DGAT2i + ACCi, compared to placebo, and the coadministration of DGAT2i + ACCi relative to DGAT2i alone, in participants with worsening of biopsy endpoint components		Proportion of participants with worsening in liver biopsy endpoint components based on assessment by sponsor-identified central pathologist(s) at Week 48 – • Progression of fibrosis by ≥1 stage • Worsening of ≥2 points in Total NAS

For ***all*** endpoints, baseline is defined as the evaluable result closest *prior* to dosing on Day 1/Visit 5

Overall Design: This is a multicenter, multinational, randomized, double-blind, double-dummy, placebo-controlled, dose ranging/finding, up to 9-arms, parallel-group, evaluation of DGAT2i alone, and DGAT2i + ACCi – refer to Schema offered in Section 1.2, below.

Number of Participants: Approximately 350 participants (50 per arm) with biopsy confirmed NASH with F2-F3 fibrosis, as assessed by sponsor-identified central pathologist(s), will be randomly assigned to the study intervention to ensure approximately 280 evaluable participants (40 per arm) offer evaluable data for the primary objective. For participants randomized before Protocol Amendment 1 is enacted those randomized to either of the 2 QD dosing regimens of DGAT2i alone will remain in the study but will be switched to the corresponding BID dosing regimen of DGAT2i alone, maintaining the assigned total daily dose and the double-blind, double-dummy design.

Intervention Groups and Duration: Participants will be randomized in a balanced ratio, using a computer-generated randomization code, to receive either double-blind, double-dummy placebo, 1 of 4 doses/dosing regimens of DGAT2i alone, ***or*** 1 of 2 dose-levels of DGAT2i + ACCi for a treatment duration of up to 48 weeks. A computer-generated randomization code using the method of random permuted blocks will be utilized to assign participants to 1 of the 9 (Original Protocol) or 7 (Protocol Amendment 1) study interventions on Day 1/Visit 5. Participants randomized under the Original Protocol will remain randomized under Protocol Amendment 1 – refer to Table 3 for details on management of the double-blinded treatment assignment between Original and Amendment 1 of this protocol.

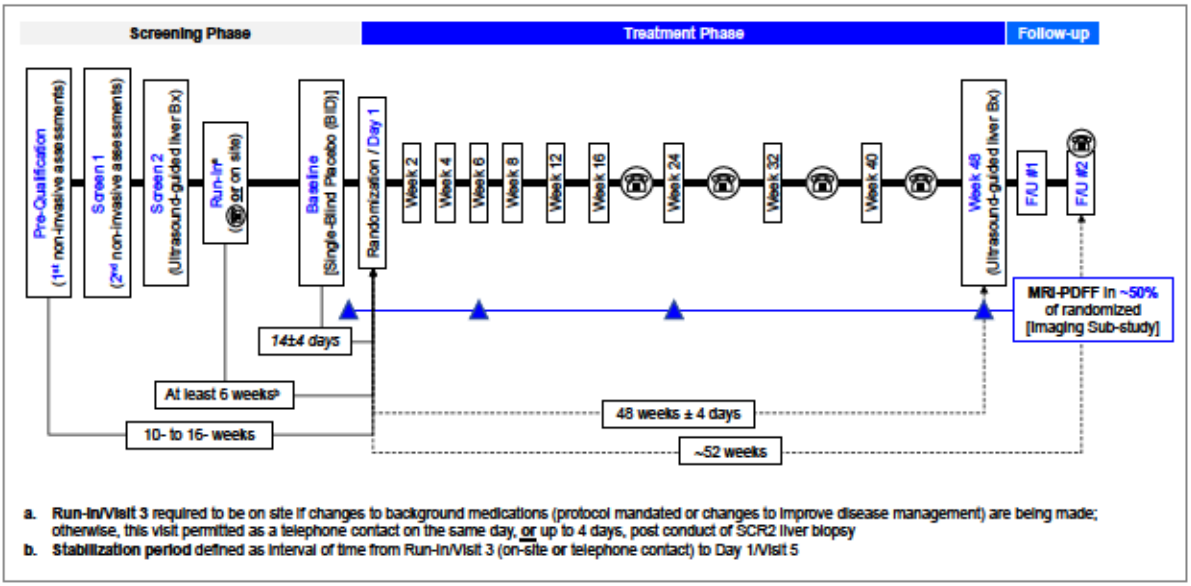
Data Monitoring Committee or Other Independent Oversight Committee: Three different Committees are envisioned – (1) independent unblinded E-DMC; (2) independent blinded Adjudication Committee; and (3) blinded Steering Committee.

Statistical Methods: The estimated sample size is driven by the characterization of dose response and treatment effect using a Bayesian E_{max} study design and modelling approach, which will utilize weakly informative priors for model parameters and will provide the ability to make more precise comparisons between treatment arms. It is estimated that a total sample size of 350 participants will give acceptable probabilities to make decisions about the dose response in the population being studied based on simulation studies. At the theoretical E_{max} of 0.6 (ie, a 60% responder rate), there would be enough precision to show a greater than 24% difference in the primary endpoint responder rate between placebo and the second highest BID dose of DGAT2i (ie, 150 mg BID) with a probability of at least 89%. In addition, this sample size will provide adequate precision to assess whether DGAT2i + ACCi provides a higher responder rate than DGAT2i monotherapy with a probability of 82% if the true effect size is at least 6%.

The planned statistical analyses for the primary, and key secondary endpoints are outlined above within the description of the estimands.

1.2. Schema

The detailed set-up of the study is summarized below –



1.3. Schedule of Activities

The *two* SoA tables provide an overview of the protocol visits and procedures. Refer to Section 8 of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA tables, in order to conduct evaluations or assessments required to protect the well-being of the participant.

SoA-Table A1: Procedures in Study C2541013

Visit Identifier	**PreQ**	**SCR1**	**SCR2**	**Run-In**	**Baseline**	**Treatment Phase** [All procedures *except* FibroScan®, MRI-PDFF and liver biopsy *before* morning dose of study intervention ±conmeds, *when applicable*]															**Follow -up**		**IP D/C or Study D/C[c]**
Weeks[a] Relative to Dosing on Day 1				**-6**	**-2**	**0**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**50**	**52[b]**	
Visit #	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	
On-site (x) [*with* Telephone (T)[b]] visits	x	x	x	x or T	x	x	x	x	x	x	x	x	T	x	T	x	T	x	T	x	x	T	x
Informed consent & demography	x	x																					
(Update) Medical & Medication history	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ultrasound-guided liver biopsy[d]			x																	x[e]			x[f]
Liver fat and stiffness (via FibroScan®)[d]	x	x			x[e]				x		x			x		x		x		x[e]			x[g]
Liver MRI-PDFF (Imaging Substudy *only*)[d]					x[e]				x					x						x[e]			x[g]
Physical Exam[h]	x	x			x	x	x	x	x	x	x	x		x		x		x		x	x		x
Assess alcohol intake (AUDIT questionnaire)	x	x				x														x			x
Assess correct use of contraception, *where applicable*				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Counseling on diet/exercise guidelines				x		x																	
Open-ended inquiry for adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Single supine 12-lead ECG	x	x			x	x								x						x	x		x
Single seated vitals (BP & pulse rate) and body weight	x	x			x	x	x		x		x			x		x		x		x	x		x
Registration of visit in study (via IRT)	x	x		x	x	x	x	x	x	x	x	x		x		x		x		x	x	x	x
Study intervention (IP) taken with *morning* meal					x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Dispensation[i] (via IRT) of study intervention (IP)					x	x	x	x	x	x	x	x		x		x		x					
Witnessed on site dosing of study intervention (IP)					x	x	x	x	x	x	x	x		x		x		x		x			
Compliance check[j] of *returned* study intervention (IP)						x	x	x	x	x	x	x		x		x		x		x			x
Continued administration of study intervention (IP)[i]					x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
NASH-Check					x									x						x			
NASH Symptoms, PGI-S, PGI-C, PROMIS Fatigue[k]					x						x			x			x			x			

SoA-Table A1: Procedures in Study C2541013

Visit Identifier	PreQ	SCR1	SCR2	Run-In	Baseline	Treatment Phase [All procedures *except* FibroScan®, MRI-PDFF and liver biopsy *before* morning dose of study intervention ±conmeds, *when applicable*]															Follow-up		IP D/C or Study D/C[c]
Weeks[a] Relative to Dosing on Day 1				-6	-2	0	2	4	6	8	12	16	20	24	28	32	36	40	44	48	50	52[b]	
Visit #	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	

a. Defined **relative to Day 1** with permitted ± 4-day window for each visit starting at Visit 4/Baseline; for example: Week -2 = 14 (±4) days before Day 1; Week 4 = 28 (±4) days post Day 1
b. Run-In Visit required to be on site if changes to background medications are being made – otherwise, Run-In Visit permitted as a telephone contact on the same day, or up to 4 days, post conduct of SCR2 liver biopsy; **post randomization**, telephone contact visits can be switched to on-site visits for follow-up of TEAEs and/or abnormal laboratory tests; Week 52 visit at ≥28- and ≤35- days post last dose of study intervention
c. Procedures to be performed as soon as practically possible after decision to stop study intervention but stay in study with continuation of scheduled visits **or** permanently withdraw from study
d. Procedure performed following ≥4 hour fast, as part of site visit **or** separate visit(s) to Imaging/Radiology facility; attempts to be made to perform procedures at the same time of day ±2-hours
e. Baseline assessment performed between Visit 4/Baseline and Day 1; end-of-study assessment performed **up to** 2 days post last dose of study intervention
f. Procedure performed **either** at time of decision to stop study intervention if ≥24 weeks post Day 1 **or** at Week 48 while off study intervention but continuing scheduled visits
g. Procedures performed **only if** decision to stop study intervention but stay in study with continuation of scheduled visits **or** permanently withdraw from study was made ≥24 weeks post Day 1
h. Full PE at PreQ and SCR1 includes arm circumference (at PreQ) and height plus waist circumference (at PreQ & SCR1); otherwise, brief PE for open AEs/abnormal laboratory tests, only
i. At Visit 4/Baseline reflects single-blind placebo; **starting Day 1** reflects double-blind **randomized** study intervention with **dispensation** at each scheduled on-site Visit through Week 40
j. Performed at on-site visits when study intervention is returned, only; **of note,** participants will not be offered study intervention post last scheduled dose
k. Completed by participants, at home (or on-site) on sponsor-provided ePRO device at set frequency (eg, once-a-day on selected days or over 14-day interval) as prompted by device/site (see Table 4)

SoA-Table A2: Blood and Urine Collections in Study C2541013

Visit Identifier	**PreQ**	**SCR1**	**SCR2**	**Run-In**	**Baseline**	**Treatment Phase** [All collections *before* **morning dose** of study intervention ±conmeds, *when applicable, except* those stated specifically as *post dose*]															**Follow -up**		**IP D/C or Study D/C[c]**
Weeks[a] Relative to Dosing on Day 1				-6	-2	0	2	4	6	8	12	16	20	24	28	32	36	40	44	48	50	52[b]	
Visit #	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	
On-site (x) [*with* Telephone (T)[b]] visits	x	x	x	x or T	x	x	x	x	x	x	x	x	T	x	T	x	T	x	T	x	x	T	x
Blood collection (following overnight fast of ≥8-hours) for –			No Blood *or* Urine Collections	No Blood *or* Urine Collections									No Blood *or* Urine Collections		No Blood *or* Urine Collections		No Blood *or* Urine Collections		No Blood *or* Urine Collections				
FSH (females only), serology (HBsAg, HCVAb, HIV), a1-antitrypsin, ceruloplasmin	x[d]	x[d]																					
%CDT	x[d]	x[d]			x[d]	x														x			x
Hematology, chemistry, coagulation	x[d]	x[d]			x[d]	x	x	x	x	x	x	x		x		x		x		x	x	x[e]	x
Pregnancy (females *only*)	x[d]	x[d]			x[d]	x	x	x	x	x	x	x		x		x		x		x	x	x[e]	x
Triglycerides, *direct* LDL-C, HDL-C, total cholesterol	x[d]	x[d]			x[d]	x	x	x	x	x	x	x		x		x		x		x	x	x[e]	x
HbA1C, Plasma Glucose	x[d]	x[d]			x[d]	x		x		x		x		x		x		x		x	x		
Direct VLDL, ApoA1, $ApoB_{total}$, ApoB100, ApoB48, ApoC3, ApoE					x	x		x		x		x		x		x		x		x	x		
PCSK9, plasma insulin, adiponectin, CK18-M30, CK18-M65, ProC3, ProC6, ELF test, hs-CRP					x	x		x		x		x		x		x		x		x	x		
Predose PK - DGAT2i and ACCi[f]						x	x			x	x	x				x				x			
Post dose PK - DGAT2i and ACCi[f,g]							x[g]			x[g]	x[g]	x[g]											
CCI																							
Spot urine collection for –																							
Urine drug test	x[d]	x[d]			x[d]																		
Urinalysis (and microscopy *when appropriate*)	x[d]	x[d]			x	x	x	x	x	x	x	x		x		x		x		x	x	x[e]	x
On-site pregnancy test (WOCBP *only*)					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[e]	x

SoA-Table A2: Blood and Urine Collections in Study C2541013

Visit Identifier	PreQ	SCR1	SCR2	Run-In	Baseline	Treatment Phase [All collections *before* morning dose of study intervention ±conmeds, *when applicable, except* those stated specifically as *post dose*]															Follow -up		IP D/C or Study D/C[c]
Weeks[a] Relative to Dosing on Day 1				-6	-2	0	2	4	6	8	12	16	20	24	28	32	36	40	44	48	50	52[b]	
Visit #	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	

a. Defined relative to Day 1 with permitted ± 4-day window for each visit starting at Visit 4/Baseline; for example: Week -2 = 14 (±4) days before Day 1; Week 4 = 28 (±4) days post Day 1

b. Run-In Visit required to be on site if changes to background medications are being made – otherwise, Run-In Visit permitted as a telephone contact on the same day or up to 4 days post conduct of SCR2 liver biopsy; ***post randomization***, telephone contact visits can be switched to on-site visits for follow up of TEAEs and/or abnormal laboratory tests; Week 52 visit at ≥28- and ≤35- days post last dose of study intervention

c. Procedures to be performed as soon as practically possible after decision to stop study intervention but stay in study with continuation of scheduled visits or permanently withdraw from study

d. Test results to be reviewed by medically qualified site staff and deemed acceptable before progression to next visit; for example: PreQ results must be reviewed prior to conduct of SCR1

e. Collections to occur only if visit is an on-site visit; collections to be skipped if visit is via telephone contact

f. In addition to blood collection, date and time of blood draw and date/time of previous two doses prior to each blood draw related to PK to be captured as part of sites' source documents

g. Collection to occur between 0.5-1.5 hours post dose (at Week 2 and Week 8 visits), between 1.5-2.5 hours post dose (at Week 12 visit), and between 3-8 hours post dose (at Week 16 visit)

h. At each of these visits, test results to be reviewed by a medically qualified site staff and deemed acceptable to continue participation in study

2. INTRODUCTION

The current study aims to evaluate two, orally administered, investigational agents – PF-06865571, a small molecule that selectively inhibits DGAT2 and the coadministration of PF-06865571 with PF-05221304, a selective, reversible, inhibitor of ACC, for the treatment of NASH with liver fibrosis. In the clinical program, this is the first study to evaluate the study interventions in participants with biopsy-proven NASH with fibrosis stage 2 or 3 (referred to as F2 or F3), as assessed by sponsor-identified central pathologist(s), using the NASH CRN definition. In this document, the compounds are referred to as DGAT2i (for PF-06865571) or DGAT2i + ACCi (for PF-06865571 when coadministered with PF-05221304).

DGATs catalyze the terminal step in triglyceride synthesis; specifically, the esterification of a fatty acid with DAG resulting in the formation of triglyceride.[1] In mammals, 2 structurally unrelated DGAT enzymes (DGAT1 and DGAT2) have been characterized. DGAT1 is highly expressed in the intestine and plays a central role in fat absorption[2] whereas DGAT2 is highly expressed in liver and adipose.[3] DGAT2i is postulated to decrease hepatic triglyceride synthesis and hepatic lipid burden in NAFLD and NASH. Based on observations in nonclinical studies conducted, it is hypothesized that DGAT2i will impact both physiological drivers contributing to NASH via direct inhibition of liver triglyceride synthesis, as well as adaptive responses leading to reduction in hepatic DNL. Following 2 weeks of dosing in participants with NAFLD, DGAT2i has been shown to reduce liver fat in a dose-responsive manner.

ACC is a biotin carboxylase that catalyzes the ATP dependent condensation of acetyl-CoA and carbonate to form malonyl-CoA.[4] Inhibition of ACC stimulates fatty acid oxidation, suppresses hepatic DNL, and reduces steatosis in animal models and in humans.[5] ACCi has been shown to decrease hepatic DNL (in healthy participants following 14-days of dosing), reduce liver steatosis (in participants with NAFLD), as well as reduce markers of liver inflammation (ALT, AST) and markers of apoptotic activity (CK18-M30 and CK18-M65), in participants with presumed NASH following 16 weeks of dosing. However, these potentially beneficial effects, in participants with NAFLD/presumed NASH, were accompanied with marked elevations in fasted serum triglycerides, a known consequence of hepatic ACC inhibition[5], and other lipid parameters (ie, reductions in direct LDL-C, HDL-C, apolipoprotein A1 along with increases in non-HDL, VLDL, apolipoprotein B, C3, and E, and no change in total cholesterol) which prohibit administration of ACCi alone. In nonclinical model of NAFLD/NASH, coadministration of DGAT2i + ACCi has been shown to be more efficacious at lowering hepatic steatosis, and reducing inflammation and fibrosis endpoints, than either DGAT2i or ACCi alone. In addition, coadministration of DGAT2i + ACCi fully reversed the increases in circulating triglycerides observed with ACCi alone – overcoming the known mechanistic consequence of hepatic ACCi thought to be a result of sterol regulatory element binding protein activation. Clinically, the effect of ACCi alone on serum triglycerides has been shown to be mitigated following 6-week of dosing of DGAT2i + ACCi in participants with NAFLD – while maintaining effective reduction in hepatic steatosis.

It is anticipated that via coadministration of DGAT2i + ACCi, hepatic lipid metabolism will be modulated in distinct and complementary ways, potentially resulting in greater efficacy than DGAT2i administered alone. DGAT2i alone and DGAT2i + ACCi are currently being developed for the treatment of NASH with liver fibrosis. ACCi alone is not planned for evaluation in this study given the anticipated adverse downstream consequence of inhibiting hepatic DNL including the already identified adverse reaction of elevated serum triglyceride and accompanying changes in other lipid parameters which are undesirable given their potential implications for long term cardiometabolic health unless sufficiently mitigated especially considering the population with NASH already may have underlying dyslipidemia and are at an increased cardiovascular risk.[6]

2.1. Study Rationale

The current study is the first clinical trial specifically designed to evaluate the effect of two, orally administered, investigational agents – DGAT2i alone, administered BID, and DGAT2i + ACCi administered BID (compared to placebo) – on resolution of NASH or improvement in liver fibrosis, as assessed histologically (via liver biopsy). Additionally, exploratory assessment of non-invasive imaging-based and blood-based collections are planned to enable potential identification of non-invasive markers of disease and/or treatment response – in the target adult population.

The study includes an evaluation of dose-ranging, dose-finding with the study intervention administered orally, twice-daily for up to 48 weeks, with the participants randomized to 1 of 9 (Original Protocol) **or** 1 of 7 (Protocol Amendment 1) treatment arms. Participants will be assigned double-blind, double-dummy administration of placebo, 1 of up to 6 doses/dosing regimens of DGAT2i alone, or 1 of 2 dose-levels of DGAT2i + ACCi – refer to Table 3. The primary objective *includes* evaluation of the effect of DGAT2i and DGAT2i + ACCi on liver histology with a key secondary objective being characterization of the safety/tolerability in the target population – ie, participants with biopsy-proven NASH with F2 or F3 fibrosis, as assessed by sponsor-identified central pathologist(s). The observed data from this study, combined with the totality of the data generated in the program, will be utilized to refine dose(s), and dosing regimens to take forward into Phase 3.

2.2. Background

The World Gastroenterology Organization lists NAFLD and NASH as the most important conditions contributing to the global health burden due to liver diseases, with NASH acknowledged as a potentially fatal condition leading to cirrhosis, liver failure, and HCC.[6] NASH is diagnosed clinically by liver biopsy demonstrating steatosis, inflammation, and cytological ballooning of liver hepatocytes, often with varying degrees of fibrosis. NASH progresses with increasing severity of fibrosis, with cirrhosis developing in a subset of participants[7] and a common complication of cirrhosis being HCC.[8] NASH is a subset of NAFLD (defined as presence of ≥5% hepatic steatosis in the absence of other liver disease etiologies)[9,10] that is associated with increased all-cause mortality, cirrhosis and end stage liver disease, increased cardiovascular mortality, and increased incidence of both liver related and non-liver related cancers.[7,8] Patients with NASH may be asymptomatic or have

non-specific symptoms such as fatigue, despite having significant disease on liver biopsy and associated risk for progression to cirrhosis and liver-related mortality.

In a meta-analysis, the global prevalence of NAFLD was estimated at 25%, with the prevalence of NASH in the subset with biopsy-proven NAFLD assessed at 59%.[9] The majority of the population with NAFLD has simple steatosis which has, in general, a benign clinical course. A proportion of participants with NAFLD progress to having hepatocellular ballooning and lobular inflammation – taking close to a decade to progress from 1 stage to the next and 30-40 years to develop cirrhosis; however, a smaller subset of participants progress very rapidly (within 10 years) to liver cirrhosis from NAFLD.[9] Patients with NASH may be asymptomatic or have non-specific symptoms such as fatigue, despite having significant disease on liver biopsy and associated risk for progression to cirrhosis and liver-related mortality. The 5-year (67%) and 10-year (38%) survival rates in participants with NASH is significantly different than in those with NAFLD.[6] The pooled liver-specific and overall mortality incidence rate estimates among those with NAFLD were calculated at 0.8 and 15.4, respectively, per 1,000 person-years. In contrast, amongst the population with NASH, the incidence rate estimates were 11.8 (liver-specific) and 25.6 (overall) mortality.[9]

Elevated rates of hepatic DNL have been reported to be a distinctive characteristic of NAFLD.[10] Clinically, those with elevated liver fat showed a more than 3-fold increase in the rate of hepatic DNL relative to participants with normal liver fat, but no differences between the groups were detected in adipose FFA flux or in production of VLDL from FFAs. Furthermore, as exemplified by other metabolic disorders (eg, type 2 diabetes, dyslipidemias, etc), it is possible that a single drug may be insufficient to successfully treat NASH and therefore, combination therapy is being considered as an early intervention strategy. Moreover, it is unknown if the effect observed on liver fat will translate to clinically meaningful improvement in histological endpoints on biopsy. As designed, this protocol permits testing coadministration of DGAT2i + ACCi which is anticipated to modulate hepatic lipid metabolism in distinct and complementary ways, suggesting that coadministration may provide greater efficacy than DGAT2i alone while mitigating the observed elevations in serum triglycerides (and other adverse lipid-related changes) observed with ACCi alone.

2.2.1. Nonclinical Overview

DGAT2i and ACCi have each individually been evaluated in a comprehensive nonclinical safety package that included CCI and CCI toxicity studies up to CCI and CCI months duration, respectively, and in reproductive and developmental toxicology studies in CCI and CCI, and together (ie, DGAT2i + ACCi) in combination toxicity studies in CCI up to CCI weeks in duration.

For DGAT2i alone, CCI findings were identified in CCI or CCI. At the NOAEL in the CCI study in CCI, exposure margins relative to a highest clinical dose of 300 mg BID were CCI and CCI the CCI human C_{max} and AUC_{24}, respectively. At the NOAEL in the CCI study in CCI, exposure margins were CCI and CCI the CCI human C_{max} and AUC_{24}, respectively.

For ACCi alone, all adverse findings were related to the [redacted]. At the NOAEL in the [redacted] study in [redacted], exposure margins relative to the highest clinical dose of [redacted] mg/day (with most conservative QD dosing and margins for C_{max}) were [redacted] and [redacted], the predicted human [redacted] C_{max} and AUC_{24}, respectively, and at the NOAEL in the [redacted] study in [redacted] exposure margins were [redacted] and [redacted] the predicted [redacted] human C_{max} and AUC_{24}, respectively.

DGAT2i + ACCi were evaluated in [redacted] toxicity studies up to [redacted] duration. All findings were attributed to [redacted] were identified in [redacted] administered DGAT2i + ACCi. Exposure margins in the [redacted] study in [redacted] relative to a DGAT2i clinical dose of [redacted] were [redacted] and [redacted], the predicted human [redacted] C_{max} and AUC_{24}, respectively, and exposure margins relative to a ACCi clinical dose of [redacted] mg/day (with most conservative QD dosing and margins for C_{max}) were [redacted] and [redacted] the predicted [redacted] human C_{max} and AUC_{24}, respectively.

2.2.2. Clinical Overview

As of *the issuance of this Protocol Amendment 1*, across the clinical studies completed with DGAT2i alone ([redacted] studies), ACCi alone ([redacted] studies) and DGAT2i + ACCi ([redacted] studies), [redacted] *unique* participants have been randomized, with [redacted] ([redacted]%) exposed to placebo, [redacted] ([redacted]%) exposed to DGAT2i alone, [redacted] ([redacted]%) exposed to ACCi alone, [redacted] ([redacted]%) exposed to DGAT2i + ACCi, [redacted] ([redacted]%) exposed to DGAT2i + metformin, and [redacted] ([redacted]%) exposed to metformin alone. DGAT2i alone has been evaluated as single oral doses up to 1500 mg, repeated doses up to 1800 mg/day (administered Q8H) for up to 14 days, and repeated doses of 600 mg/day (administered Q12H) for up to 6 weeks. ACCi alone has been administered at single, oral doses up to 240 mg, repeated (≤14-days) doses up to 200 mg/day (administered QD and Q12H), and repeated (≤16 weeks) doses up to 50 mg/day (administered QD). DGAT2i + ACCi has been evaluated at a single coadministered dose level of 300 mg BID (DGAT2i) + 15 mg BID (ACCi).

DGAT2i alone *or* as DGAT2i + ACCi has been evaluated in [redacted] Phase 1 studies in adults (with [redacted] participants randomized) and [redacted] studies ([redacted] Phase 1b and [redacted] Phase 2a) in participants with NAFLD (with [redacted] randomized). ACCi alone has been evaluated in [redacted] Phase 1 studies in adults (with [redacted] participants randomized) and one Phase 2a, dose-ranging study in participants with NAFLD (n=305, randomized including n=208 with presumed NASH).

Administration of DGAT2i alone has been found to be [redacted] Upon repeated administration of DGAT2i, across the 20-fold dose range evaluated (ie, 90 to 1800 mg/day), TEAEs reported in ≥[redacted] participants across all arms evaluated were headache ([redacted]%), diarrhea ([redacted]%), fatigue ([redacted]%), pruritus ([redacted]%), abdominal pain ([redacted]%), and nausea ([redacted]%). Upon repeated administration of ACCi, across a 100-fold dose range evaluated (ie, 2- to 200- mg/day), the all-causality TEAEs reported in ≥[redacted]% of participants were headache ([redacted]%), diarrhoea ([redacted]%), hypertriglyceridaemia ([redacted]%), and nausea ([redacted]%).

Given DGAT2i is a CCI , as expected, CCI were noted. Dosing with ACCi alone resulted in CCI refer to Section 2.3.1. Coadministration of DGAT2i + ACCi has been shown to CCI to either agent administered alone. However, on average, DGAT2i + ACCi has been shown to mitigate the ACCi-induced elevations in serum triglycerides, ApoC3, and non-HDL. No apparent abnormalities were noted in other safety-related assessments such as CCI with DGAT2i, ACCi, and DGAT2i + ACCi.

Upon repeated dosing of DGAT2i with standard meals, C_{max} was achieved at CCI post dose. Steady-state plasma concentrations were achieved by CCI , and the mean terminal CCI Dosing in the fasted state resulted in lower exposures (ie, CCI and CCI than when a CCI mg DGAT2i dose was administered with a standard meal). Following oral dosing of ACCi with a high-fat/high-caloric meal, C_{max} was achieved at CCI post-dose, and the mean terminal CCI There was CCI on exposure with dosing of ACCi in the fasted versus fed state. Coadministration of DGAT2i (CCI) and ACCi (CCI) has been shown to result in a slight CCI in the systemic exposure of ACCi – with adjusted geometric mean (90% CI) of CCI (for C_{max}) and CCI CCI (for AUC_{tau}). There was CCI on the systemic exposure of DGAT2i, when coadministered with ACCi, with adjusted geometric mean CCI (for C_{max} and AUC_{tau}).

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs with DGAT2i alone, DGAT2i + ACCi, and ACCi alone can be found in the IB for DGAT2i and CCI for ACCi, which will serve as the CCI SRSDs for this study.

A high level summary of potential risks as well as benefits are offered in Section 2.3.1 and Section 2.3.2, below.

CCI

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention – DGAT2i		
CCI		

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
CCI		
Study Intervention – ACCi (as part of DGAT2i + ACCi)		
CCI		

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
CCI		
Study Procedures		
Conduct of up to 2 liver biopsies during study	Procedure is relatively safe with <1% risk of major complications[11]; potential risks include – • Increased anxiety – especially with 2nd biopsy • Pain which can last for days post procedure • Bleeding from needle biopsy site	• Permitting pre-procedure use of anxiolytics to manage anxiety • Allowance for use of analgesics for post procedure pain management • Study requirement of post-procedure close observation period of at least 2-4 hours for any abdominal symptoms, bruising, *plus* avoiding heavy lifting for ≥48 hours post procedure • After 1st biopsy and before randomization, actively elicit participants' willingness to undergo 2nd biopsy
Conduct of 4 MRI-PDFF assessments during study (in 50% of participants in Imaging sub-study)	Procedure is relatively safe; potential risk for non-evaluable images include – • Too much motion, for example, due to increased anxiety, claustrophobia • Ferric implants/devices, paramagnetic objects within/on body, ferric-containing tattoos in area of interest (abdomen, chest, arms)	• Permitting pre-procedure use of anxiolytics to manage anxiety • Excluding participants, from Imaging sub-study, if they have contraindications for MRI • Clear communication via ICD of preparation for each visit *including* duration of fast before procedures/visits

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	• Minimum duration of a priori fast *not* followed	
Other Factors Potentially Impacting Study Results		
Eligible population must have NASH (ie, total NAS score ≥4 with ≥1 score for steatosis, inflammation, and ballooning *plus* fibrosis stage of either F2 or F3)	Assessment of primary endpoint could be potentially compromised if non-eligible population is randomized	• Triage strategy with *double-confirmation* via non-invasive tests[12] used as part of eligibility to confirm presumed NASH status ***before*** proceeding with screening/baseline liver biopsy • Standardization of biopsy acquisition, processing, staining employed to ensure evaluable tissue (limit non-evaluable tissue sample collections) • Determination of eligibility based on liver biopsy made centrally by 2 pathologists with consensus requirement between pathologists' mandatory
Distinction of drug-induced liver injury from disease-related baseline elevations in LFTs	Population eligible likely to have elevated ALT and AST (though not Alkaline phosphatase, total bilirubin)	• Study requires *double-confirmation* of stable ALT, AST, alkaline phosphatase (ie, ≤50% variability[13]) plus total bilirubin ≤ULN ***before*** proceeding with screening/ baseline liver biopsy

Coadministration of DGAT2i + ACCi, based on completed toxicity studies in CCI and CCI does CCI findings above and CCI In Study C2541013, any adverse clinical impact of the above findings are expected to depend on the severity of the potential reaction, and are minimized through – **(1)** the proposed frequent visits to site to permit close oversight of participants' safety via medical monitoring of a range of clinical assessments including safety-related laboratory tests, 12-lead ECGs, vitals, assessment of AEs; **(2)** inclusion of provisions for management of glycemic control (refer to Appendix 10) and the CCI – namely, CCI (refer to Appendix 11) CCI (refer to Appendix 12); and **(3)** institution of an E-DMC (refer to Section 9.6) to undertake unblinded, periodic reviews of the safety data, while the study is on-going, and make recommendation(s) as to whether 1 or more arms should be paused/discontinued amongst the planned activities.

2.3.2. Benefit Assessment

The current study is the first time that DGAT2i and DGAT2i + ACCi is being administered to the target population – ie, those with biopsy-confirmed NASH and liver fibrosis stage of F2 or F3, as assessed by sponsor-identified central pathologist(s). For the participants of this study, close monitoring of their medical condition and safety will occur as outlined in this protocol. In the Original Protocol, for every 9 participants randomized, 8 who receive

DGAT2i or DGAT2i + ACCi may potentially derive benefit from the desired pharmacology, namely, reversal of hepatic steatosis, decrease in hepatic inflammation and improvement in hepatic fibrosis. Following implementation of Protocol Amendment 1, for every 7 participants randomized, 6 who receive DGAT2i or DGAT2i + ACCi may potentially derive benefit. Those randomized to placebo (1 in every 9 [Original Protocol] or 1 in every 7 [Protocol Amendment 1] participants) are not expected to obtain any specific benefit, beyond close monitoring of their medical condition and safety. All participants will receive general, standard-of-care guidance/counseling regarding the overall benefits of diet/exercise.

2.3.3. Overall Benefit/Risk Conclusion

Accounting for the measures taken to minimize risk to participants enrolled in this study, the potential risks identified in association with DGAT2i and DGAT2i + ACCi are justified by the anticipated benefits that may be afforded to participants with biopsy-proven NASH with F2 or F3 fibrosis.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Estimands	Endpoints
Primary:		
To evaluate the effect of a range of DGAT2i doses administered alone, and coadministration of DGAT2i + ACCi, compared to placebo, and the coadministration of DGAT2i + ACCi relative to DGAT2i alone, ***in participants with biopsy confirmed NASH and fibrosis, on resolution of NASH without worsening of fibrosis or improvement in fibrosis by ≥1 stage without worsening of NASH, or both***	Using a composite estimand strategy in participants with biopsy-confirmed NASH and fibrosis, estimate the treatment effect of DGAT2i doses administered alone and coadministration of DGAT2i + ACCi relative to placebo, and coadministration of DGAT2i + ACCi, relative to DGAT2i alone, in terms of the proportion of 'clinical responders', defined as participants achieving centrally adjudicated: resolution of NASH without worsening of fibrosis or improvement in fibrosis by ≥1 stage without worsening of NASH, or both, at Week 48 and treating all cases of withdrawal from treatment for lack of efficacy or toleration as non-responders • All treatment effect contrasts will be obtained through fitting the Bayesian dose-response and/or exposure-response models with a logit transformation, or logistic regression models	Proportion of participants achieving resolution of NASH without worsening of fibrosis ***or*** improvement in fibrosis by ≥1 stage without worsening of NASH ***or*** both, based on assessment by sponsor-identified central pathologist(s), at Week 48
Secondary:		
To evaluate the effect of a range of DGAT2i doses administered alone, and coadministration of DGAT2i + ACCi, compared to placebo, and the coadministration of DGAT2i + ACCi relative to DGAT2i alone, on ***liver fat***	Using a hypothetical estimand strategy, in participants with biopsy-confirmed NASH and fibrosis, estimate the treatment effect of DGAT2i doses administered alone and coadministration of DGAT2i + ACCi relative to placebo, and coadministration of DGAT2i + ACCi, relative to DGAT2i alone, in terms of the population level average percentage change from baseline in liver fat (assessed via MRI-PDFF) at Week 48, assuming all participants had remained in the trial and received treatment as planned without withdrawal up to 48 weeks. Endpoint data collected after treatment withdrawal will be censored. • All treatment effect contrasts will be obtained through fitting the Bayesian dose-response	Percent change in liver fat (assessed via MRI-PDFF in substudy population), at Week 48

Objectives	Estimands	Endpoints
	and/or exposure-response models, or ANCOVA models	

To evaluate the effect of a range of DGAT2i doses administered alone, and coadministration of DGAT2i + ACCi, compared to placebo, and the coadministration of DGAT2i + ACCi relative to DGAT2i alone, ***in participants achieving improvement in different responder definitions***	Using a composite estimand strategy in participants with biopsy-confirmed NASH and fibrosis, estimate the treatment effect of DGAT2i doses administered alone and coadministration of DGAT2i + ACCi relative to placebo, and coadministration of DGAT2i + ACCi, relative to DGAT2i alone, in terms of the proportion of 'clinical responders', defined as participants achieving centrally adjudicated resolution of NASH without worsening of fibrosis at Week 48 and treating all cases of withdrawal from treatment for lack of efficacy or toleration as non-responders
	• All treatment effect contrasts will be obtained through fitting the Bayesian dose-response and/or exposure-response models with a logit transformation, or logistic regression models
	• Similar estimands will be assessed for:
	  • Improvement in fibrosis by ≥1 stage, without worsening of NASH
	  • Improvement in fibrosis by ≥2 stages, without worsening of NASH
	  • Improvement of ≥2 points in Total NAFLD Activity Score (NAS)
		Proportion of participants achieving improvement in different responder definitions based on assessment by sponsor-identified central pathologist(s) at Week 48 –
		• Resolution of NASH, without worsening of fibrosis
		• Improvement in fibrosis by ≥1 stage, without worsening of NASH
		• Improvement in fibrosis by ≥2 stages, without worsening of NASH
		• Improvement of ≥2 points in Total NAS

To assess the ***safety and tolerability*** with a range of DGAT2i doses administered alone, and coadministration of DGAT2i + ACCi, compared to placebo, and the coadministration of DGAT2i + ACCi relative to DGAT2i alone		Assessment of TEAEs, safety-related clinical laboratory tests, vital signs, and 12-lead ECGs, over time up to Week 48
Tertiary/Exploratory:		
To evaluate the effect of a range of DGAT2i doses administered alone, and coadministration of DGAT2i + ACCi, compared to placebo, and the coadministration of DGAT2i + ACCi relative to DGAT2i alone, in participants with worsening of biopsy endpoint components		Proportion of participants with worsening in liver biopsy endpoint components based on assessment by sponsor-identified central pathologist(s) at Week 48 – • Progression of fibrosis by ≥1 stage • Worsening of ≥2 points in Total NAS

For ***all*** endpoints, baseline is defined as the evaluable result closest *prior* to dosing on Day 1/Visit 5

Additional tertiary/exploratory objectives and endpoints are listed in Section 9.4.7.

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, multinational, randomized, double-blind, double-dummy, placebo-controlled, dose ranging/finding, up to 9-arms, parallel-group study. The study interventions include placebo administered BID, 4 active doses of DGAT2i with total daily dose split and

administered BID, 2 active doses of DGAT2i with total daily dose administered QD in the Original Protocol (with dummy placebo for 2nd dose each day to preserve the blind), and 2 active doses of DGAT2i + ACCi administered BID. Dosing of all arms is accommodated via administration of 3 tablets per dose, BID, and proposed using blister packed supplies to minimizing dosing errors and enhance compliance – refer to Table 3 in Section 6; with an added measure wherein sponsor-provided ePRO devices to be provided to each participant [refer to Section 8.1.3] will be auto-programmed to offer *periodic* reminders to enhance compliance with dosing of study interventions.

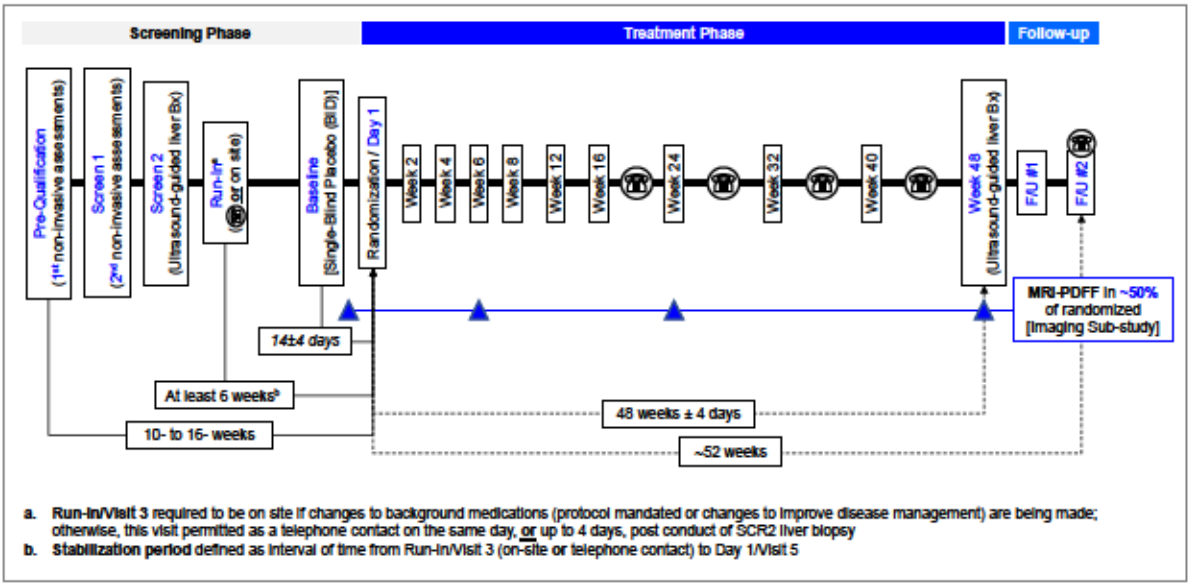
Determination of eligibility will occur via a sequential, 2-step process starting with PreQ. Participants identified to be eligible based on PreQ will transition to the main study (ie, SCR1). Once confirmed to be eligible based on the non-invasive assessments, participants will progress to SCR2 and undergo liver biopsy. The ***double-confirmation*** via non-invasive assessments (at PreQ and SCR1) will enable progression of only the selected subset of participants, more likely to have biopsy-proven NASH with F2-F3 fibrosis on biopsy, as assessed by sponsor-identified central pathologist(s).

Once confirmed to be eligible, participants will be informed of the screening/baseline liver biopsy results at the next ***on-site*** visit (ie, either Run-In/Visit 3 ***or*** Baseline/Visit 4). If changes in background medications (either protocol mandated or to improve disease management) are planned, the Run-In/Visit 3 must be an on-site visit conducted post availability of SCR2 liver biopsy results from the sponsor-identified central laboratory. Stabilization of concomitant/ background treatment(s) required for at least 4-weeks before transition to Baseline/Visit 4 – refer to Section 6.5. ***All*** eligible participants will complete the Run-In period, followed by Visit 4/Baseline.

On Day 1/Visit 5, participants who meet randomization criteria (Section 5.3) will be assigned to receive 1 of 9 (Original Protocol) **or** 1 of 7 (Protocol Amendment 1) double-blind, double-dummy regimens for a duration of up to 48 weeks (336±4 days).

A total of 22 visits (from PreQ to 2nd follow-up visit) – encompassing a combination of on-site visits and telephone contacts – are envisioned. For a given participant, time in the study may range from 62 weeks (minimum) to potentially 68 weeks (maximum) – refer to Figure 1.

Figure 1. Overall Study Design



Approximately 350 participants (50 per arm) with biopsy confirmed NASH with F2-F3 fibrosis, as assessed by sponsor-identified central pathologist(s), will be randomly assigned to the study intervention to ensure approximately 280 evaluable participants (40 per arm) offer evaluable data for the primary objective of the study.

4.2. Scientific Rationale for Study Design

Reduction in hepatic steatosis with DGAT2i alone, ACCi alone, and DGAT2i + ACCi have been shown in participants with NAFLD with dosing of the intervention for as little as 2 weeks (DGAT2i alone) and 6 weeks (DGAT2i alone plus DGAT2i + ACCi), and up to 16 weeks (with ACCi alone). Translation of effect on liver steatosis to histological improvement in NASH or liver fibrosis is the primary focus of the current study and hence the primary endpoint is proposed as proportion of participants achieving NASH resolution (without worsening fibrosis) *or* improvement in fibrosis (without worsening NASH) *or* both. Acknowledging the primary pharmacology of DGAT2i and DGAT2i + ACCi targets hepatic lipid synthesis hypothesized to result in reducing inflammation and fibrosis, the duration of dosing with study interventions is proposed as 48 weeks, in line with multiple regulatory guidance documents for agents in development for the treatment of NASH with liver fibrosis.

In the current study, eligible population is limited to those with biopsy-proven NASH with fibrosis stage F2 or F3, standardized to the NASH-CRN definition[14], and in line with natural history studies indicating severity of liver fibrosis on histology being the only independent predictor of liver-related morbidity and mortality[15]. However, this study includes two distinct phases with non-invasive assessments to identify those more likely to have NASH with fibrosis before participants are progressed to the screening/baseline liver biopsy. As such, two separate informed consents will be obtained – 1st limited to PreQ visit only; and 2nd for the main study only in those deemed to meet eligibility criteria based on non-invasive procedures completed at PreQ (plus, *an additional provision/flexibility* for those participating

in Imaging Substudy to offer dedicated consent for this procedure closer to Baseline MRI-PDFF ***or*** at the time of consent obtained at SCR1). Population identified to be considered for PreQ will include those with common conditions identified as risk factors associated with NAFLD.[16] In addition, eligible population identified to be overweight, obese, as well as morbidly obese though upper limit of acceptable BMI capped at 45 kg/m^2. Between the PreQ and SCR1 visits, many of the non-invasive procedures and clinical laboratory tests assessed are identical – this is motivated by the intent to confirm that the population progressed to liver biopsy at SCR2 is consistently characterized. As a measure of additional diligence and as an attempt to remove variability due to differences from laboratory-to-laboratory, the clinical laboratory tests assessed at PreQ and SCR1 are proposed to be analyzed by the sponsor-identified central laboratory. The non-invasive assessments to narrow the population ultimately undergoing screening/baseline liver biopsy consist of ***double-confirmation*** between assessment at PreQ and SCR1 of:– (a) blood-based markers of liver function (ie, ALT, AST, alkaline phosphatase, total bilirubin) and ensuring participants have stable results (defined by ≤50% variability in ALT/AST/alkaline phosphatase[13] plus total bilirubin ≤ULN, unless Gilbert's syndrome); (b) consistent presence of concomitant risk factors associated with NAFLD ; ***and*** (c) evaluation of FAST™ score[12] (a composite of FibroScan® derived CAP™ and VCTE™ plus AST) to identify at-risk participants of progressive NASH. The FAST™ score threshold of ≥0.30 for eligibility was derived using individual-level data co-owned by EchoSens, the manufacturer of FibroScan®, and shared with the sponsor for the purposes of designing this protocol. The threshold of CAP™ ≥280 dB/m ***plus*** VCTE™ between 8.0 and 20.0 kPa, inclusive, is permitted to account for the ***limited cases*** where ***evaluable*** FibroScan® results are highly suggestive of presumed NASH with fibrosis[17] but the FAST™ score is below 0.30.

In this study, based on a combination of thorough medical history (including assessment of ethanol intake and administration of the *interview-version* of the AUDIT 10-item questionnaire[18]), and clinical laboratory tests (including GGT and %CDT), medically-qualified site-staff will be required to rule-out alcohol-based as well as other causes of hepatic steatosis/inflammation/fibrosis, and ensure that the population enrolled is confirmed, as best as possible, to have NASH with F2-F3 liver fibrosis.[19] These assessments (AUDIT and %CDT) will be re-assessed prior to randomization and at end of dosing to confirm that while in the study alcohol intake remained in moderation. Participants with previously confirmed genetic polymorphisms, for example, PNPLA3 carriers, are eligible given these polymorphisms are known to modify/increase risk for steatohepatitis but do not by themselves cause steatohepatitis.

An explicit intent in this study is to CCI those with CCI impairment CCI and CCI impairment (ie, CCI via specific eligibility criteria (refer to Section 5.1 and Section 5.2). This is in line with the clinical data to date showing CCI increase in plasma exposure in CCI for ACCi and DGAT2i in participants with CCI compared to healthy participants; as well as CCI confirmed to represent <CCI% of unchanged drug – for both DGAT2i and ACCi. The CCI clearance mechanism for DGAT2i and ACCi is predicted to be CCI. Thus, the

inclusion/exclusion criteria have been defined to help limit pharmacokinetic variability while also capturing a population that is characteristic of the intended target population. Blood samples (both pre- and post-dose) to permit population-pharmacokinetic analysis will be collected to further examine the effect of demographics on pharmacokinetic variability.

A priori, to permit an evaluation of potential differences in treatment response in NASH with F2 versus NASH with F3 fibrosis with DGAT2i and DGAT2i + ACCi, this study employs stratification based on degree of fibrosis (F2 vs F3). In addition, this study will identify the population with and without a diagnosis of T2DM based on HbA1C result ≥6.5% and/or current use of *approved* agents for glycemic control (Section 6.5.1). This is to permit an assessment of whether DGAT2i and/or DGAT2i + ACCi demonstrate insulin sensitization properties similar to the effect observed with ACCi alone in the 16-week, Phase 2a study in participants with NAFLD.

Beyond the assessment on histological endpoints, the current study also undertakes assessment for potential improvement on non-invasive biomarkers – both imaging and blood-based. Assessment of liver fat and liver stiffness using ultrasound-based FibroScan® in the entire population and liver fat via the validated tool for clinical assessment of hepatic steatosis[7] - MRI-PDFF (in Imaging Substudy) is planned. The blood-based parameters include markers of liver function tests (ALT, AST, Alkaline phosphatase, GGT, Total bilirubin), NASH-related biomarkers[21] (3-parameter derived ELF™ Score, marker of liver fibrosis used to track disease progression; CK18-M30 and CK18-M65, markers of apoptotic activity; ProC3, a marker of fibrinogenesis; ProC6, a marker of fibrinolysis), glycemic parameters (HbA1C, FPG, FPI, HOMA-IR, adiponectin), and fasting lipid parameters/markers of target engagement (total cholesterol, triglycerides, direct LDL-C, HDL-C, direct VLDL, apolipoprotein A1, B_{total}, B_{100}, B_{48}, C3, and E *plus* PCSK9, hs-CRP). CCI [redacted] collections is planned to enable CCI [redacted] Furthermore, recent research has indicated that there is an unrecognized symptom burden with NASH. In particular, abdominal pain, and fatigue, were identified as relevant in sponsor-conducted patient interviews and found to be responsive to histological change in a trial with obeticholic acid.[22] Inclusion of ePROs in the current study will allow testing of this hypothesis, and optimization of ePROs taken forward into Phase 3. Such data may also be valuable in supporting histology as a surrogate outcome in future health technology assessments. In this study, baseline, when obtained will be done at Visit 4/Baseline *or* while participants are receiving single-blind placebo – refer to Table 4.

For the assessment of liver fat (either via FibroScan® [in the entire population] or MRI-PDFF [in the Imaging Substudy]), participants will be required to fast (water permitted) for ≥4-hours given the ability of food to impact the results. As an additional measure to limit variability, attempts will be made to standardize the nominal time of these two assessments. The clock time of day when these assessments are made should fall within a practical window (±2-hours) relative to clock time at PreQ for FibroScan® and Baseline (ie, between Visit 4/Baseline and Visit 5/Day 1 for MRI-PDFF, in the Imaging Substudy), as much as practically possible. Serial assessments post randomization via MRI-PDFF and FibroScan® are planned to permit a mixed-model-repeated-measure analysis thereby allowing for

evaluation of drug effect longitudinally and, at each visit, including end of dosing with the study intervention – ie, Week 48/Visit 19.

While the clinical experience with DGAT2i and DGAT2i + ACCi is limited to maximum of CCI, transition to 48 weeks of dosing in the current study is deemed to be acceptable given: (a) loss-of-function mutation in DGAT2[23] – Tyr285X – phenotypically has no clinically significant presentation other than an association with decreased HDL-C, with implications of this observations unknown; (b) chronic toxicity studies with DGAT2i in CCI (up to CCI) and CCI (up to CCI) with dosing up to CCI dose (CCI) did not result in any adverse findings *plus* in toxicity study with DGAT2i + ACCi in CCI (up to CCI), findings were in line with those reported with administration of CCI; ***and*** (c) CCI was not identified with 14 day dosing at CCI than the top dose of DGAT2i in the current study (600 mg/day). Despite this safety profile, given the transition to the proposed 48 weeks of dosing in this study, measures to ensure participant safety are included – **(a)** frequent (every 2-week), outpatient visits up to Week 8/Visit 9, followed by contact with sites every 4 weeks, *either* as outpatient visits *or* telephone contact, up to Week 48/Visit 19 with provisions for unplanned visits for follow-up of AEs (refer to Section 8.3.3) and clinically significant laboratory results (refer to Section 8.2.5); **(b)** *as much as practically doable*, the use of same-day shipment of safety-related blood/urine samples to sponsor-identified central laboratory with rapid turn-around of safety-related results and management of metformin dose as well as overall glycemic control (Appendix 10); **(c)** standardization of *blinded* management of the CCI with administration of ACCi – namely CCI in CCI (refer to Appendix 11) and CCI (refer to Appendix 12); **(d)** use of adjudication committee (for liver- and CV- events) and an E-DMC (refer to Section 9.6) to undertake *unblinded* review of safety data post randomization, at a minimum, of approximately 33%, 67%, and 100% of planned total sample size in Protocol Amendment 1; and **(e)** periodic *blinded* review of safety by the sponsors' clinical team members to assess for potential trigger for additional E-DMC unblinded review(s) of cumulating safety data while the study is on-going.

Plasma exposure of ACCi following a high-fat/high-caloric breakfast was CCI relative to administration of ACCi following an overnight fast; however, plasma exposure of DGAT2i is CCI by CCI% (AUC_{inf}) and CCI% (C_{max}) when administered following an overnight fast versus with standard meal. As such, administration of the study interventions in this study will be requested to occur with the morning (and evening) meals – given the importance of regular meals to the standard-of-care diet counselling for the planned population.

For all participants, a ***stabilization period*** of at least 4-weeks ***prior*** to Baseline/Visit 4 (ie, 6-weeks prior to Day 1/Visit 5) is mandatory for stabilizing background medications (including simply compliance) and accompanying monitoring parameters in order to minimize placebo response post randomization. This can be achieved via conduct of the Run-In/Visit 3 ***either*** as –

- An on-site visit ***after*** availability of SCR2 liver biopsy results from the sponsor-identified central laboratory **if** changes to background medications *either* protocol

mandated ***or*** changes to improve disease management (refer to Section 6.5) are planned;

- ***Or*** a telephone contact on the same day, ***or*** up to 4 days, post conduct of SCR2 liver biopsy if no change in dose(s) of background medications is deemed to be clinically necessary.

In addition, a fixed, single-blind, 2-week baseline period (ie, Visit 4/Baseline to 1-day prior to Visit 5/Day 1 is included in this study with the explicit purpose of familiarizing the participants with the dosing instructions for the study intervention (refer to Table 3), and to exclude participants who are *not* compliant with the single-blind placebo prior to randomization in an attempt to minimize medications errors post randomization.

4.2.1. Participants of child-bearing potential

CCI are *not* available for DGAT2i, or DGAT2i + ACCi.

In the completed, CCI studies with DGAT2i alone and ACCi alone (and hence DGAT2i + ACCi in this study) findings have been CCI – refer to Section 2.3.1. Therefore, the **use of a** CCI **method of contraception is** CCI by females of childbearing potential - refer to Section 5.4.1 and Appendix 4 for additional details.

The potential risk of exposure, CCI, to DGAT2i or DGAT2i + ACCi in a female sexual partner of childbearing potential of a male participant in this study is CCI. As such, use of CCI is CCI in the male participants. The calculated safety margin is CCI between the estimated partner exposure due to seminal transfer and the NOAEL for CCI in nonclinical studies. The safety margin of CCI is based on applying a CCI safety factor for interspecies extrapolation and a CCI safety factor for susceptible populations.[24]

CCI will be collected and stored for CCI which may, for example, provide greater understanding of the study intervention. Comparing the CCI, CCI, and CCI of participants who respond well and those who respond poorly to treatment may help to better define the most appropriate group of participants in which to target a given treatment. Collecting CCI for CCI and retaining them in the CCI make it possible to better understand the investigational product's CCI Refer to Section 8.7 and Appendix 5, for additional details.

Providing CCI is a required study activity for study sites and participants, unless prohibited by local regulations or EC decision.

4.2.3. Participant Input Into Study Design

Patient panels/interviews were conducted to gain input from adults with (presumed) NASH on the working draft protocol. The input offered, and its' incorporation, is summarized in Table 1.

Table 1. Participant Input into C2541013 Study Design

Participant Feedback	Implementation *Planned* (or included herein)
Overall Study Design – deemed reasonable but strong desire to know rationale for – • Why study intervention might work • Risks/potential benefits • Visit schedule *and* any preparation needed ahead of each visit • Cost (and compensation) of participation, if any	As part of ICD clearly (and simply) articulate – • Mechanism of action and "reason to believe" • Balanced perspective regarding potential benefit and potential risks • Rationale for list of ***all*** planned procedures and highlighting that these are at no cost to participants • Restrictions (eg, required fasted duration) and why these are important o *Plus,* what to do if they forget to do a required pre-visit preparation (eg, arrive non-fasted, post AM dose of study intervention, have not completed ePRO) • Planned compensation structure (not simply at end of study participation)
Requirement of Liver Biopsy – *not* preferred but will do it so long as – • There is no other option • It helps their (and may be others) medical management	• Use of triage to progress only those to biopsy who are more likely to qualify for the study • Limit study to a maximum of 2 biopsies *plus* 1 of these is permitted to be a recent historical biopsy, if available, to serve as screening/baseline biopsy • Require experienced specialist who will serve as investigator to perform biopsy o Increase positive impression of participants post 1st biopsy to enable higher probability of participants interest in 2nd biopsy • Require communication of SCR2 biopsy results as reported by sponsor-identified central laboratory to be a face-to-face interaction (ie, at ***either*** the on-site Visit 3/Run-In or Visit 4/Baseline) with the investigator • Permit use of anxiolytics along with local standard-of-care for type of needle; however, dictate gauge to be limited to 1 of 2 to ensure evaluable tissue is collected – refer to Section 8.1.1
Duration of each outpatient visit *plus* need for potential visits to different locations (eg, to site, radiology, imaging facility) – • 3-4 hours is long but doable so long as schedule is known a priori • There has to be some flexibility for when to complete each visit (eg, ±1-2 days) • And there needs to be compensation for time and travel	• Visit window kept flexible from PreQ to Visit 3/Run-In – refer to Figure 1 • Each visit starting at Visit 4/Baseline devised with ± 4-day window for ease of participant and site • Allowance made for procedures that may require visits to different locations to be done over multiple days (not all on the same day) • Ensure capture of compensation for time and inconvenience, in compliance with GCP
Pill burden – 3 pills/dose x 2/day is not attractive, especially 2 being large + 1 small	• Blister pack designed with visual cues for AM vs PM dose (eg, different colors for the 3 columns covering AM dose vs PM dose)

Table 1. Participant Input into C2541013 Study Design

Participant Feedback	Implementation *Planned* (or included herein)
• But pill burden is manageable since already taking many more pills per day on a similar schedule • Like set-up of blister packs (and not bottles) • Ask that tablets be coated as they are easier to swallow	• Each blister card = 7-days of dosing • Inclusion of *periodic* dosing reminders as part of sponsor-provided ePRO device to be taken home by participants
Blood draws – do not like too many tubes drawn at a time • Interest in knowing why so many tubes are needed • Wanted results to be shared with them as study is going on (or at end of study)	• Validated DGAT2i and ACCi PK assay to permit use of CCI CCI and a CCI assay both analytes à saved CCI CCI per PK draw by combining assay • Grouped analytes to be assayed, by vendor, to limit number of tubes of blood drawn • Balance need for ensuring participant safety (ie, with inconvenience of visits and blood draws) *and* keeping them engaged (by switching on-site visits to telephone contact)
PROs – there is willingness to complete daily 2 min at-home questionnaire *plus* 20 min in-clinic questionnaire 5 times during study on electronic devices • Like idea of electronic vs paper entries • Auto-reminders would be helpful • Want to know consequence of completing late in the day • Quality and accuracy of translations from English to native language of participants important	• Implementation planned as electronic sponsor-provided devices with the added feature of reminders for ePRO completion • No plans to a priori define when on a given day ePROs should be completed • Plan to follow translation process that includes cognitive debriefing in native language to ensure cultural equivalency
Willingness to stay in study off study drug ranged along with personal motivators • Benefit needed to be there – eg, access to their data to help future treatment or management of their disease, a sense of belonging/being valued, learning of study progress • Understood commitment to study and importance of having complete data • But there is concern with having to withstand the 2nd biopsy in that case	• Aggregate level summary of study results in lay language planned at end of study – refer to Section 10.1.5 • *Pending IRB/EC approval,* plan to implement participant-focused communications; eg, key milestones in study, personalized message at key personal dates for individual participants – communicated via, *for example*, social media, e-mail, text messages, print material covering 'tips-of-the-day'

4.3. Justification for Dose

For the administration of DGAT2i as monotherapy as well as coadministration with ACCi in this study, selection of doses to be evaluated were informed by reduction in liver fat observed following 2 weeks of dosing with DGAT2i in Study C2541005, 6 weeks of dosing of DGAT2i alone, ACCi alone, and coadministration in Study C3711001, as well as 16 weeks of dosing with ACCi alone in Study C1171002.

Exposure-response analysis of reduction in liver fat and average DGAT2i concentrations observed in Study C2541005 informed DGAT2i monotherapy dose-ranging dose selection – refer to Table 2. The CCI of reduction in liver fat was estimated to be CCI . A dose of approximately 25 mg BID (50 mg total daily dose) was projected to achieve average concentrations near the CCI using a preliminary population pharmacokinetic model developed using single-dose and multiple-dose PK data from previous clinical studies with DGAT2i. However, the CCI based on the histological effect on liver is unknown despite a likely correlation between reduction in liver fat and histological changes evident on liver biopsy. A 300 mg BID dose (600 mg total daily dose) was projected to achieve CCI . Model predictions of reduction in liver fat based on CCI were also conducted. Based on these model analyses, DGAT2i doses of 25, 75, 150, and 300 mg BID were chosen for evaluation in this study.

In the Original Protocol, an evaluation of efficacy with QD administration of DGAT2i alone was also planned based on the CCI effect on liver fat at 50 mg BID in Study C2541005. DGAT2i doses of 150 mg QD and 300 mg QD were selected to compare with BID regimens at the same daily dose (75 mg BID and 150 mg BID) to permit evaluation of whether achieving a similar CCI results in CCI efficacy - Table 2. The CCI for CCI effect on hepatic fat for CCI versus CCI regimen of DGAT2i alone formed the basis for the strategic decision to deprioritize evaluation of same total daily dose – administered BID or QD via Protocol Amendment 1. With the intent to no longer pursue the scientific evaluation of QD dosing regimen, data will be analyzed by total daily dose of DGAT2i alone, regardless of whether it was administered BID or QD.

Table 2. CCI

DGAT2i Total Daily Dose (mg)	CCI			
	Placebo-Adjusted Change from Baseline (%), Median (90% CI) at 2 Weeks		Placebo-Adjusted Change from Baseline (%), Median (90% CI) at 6 Weeks	
	QD	BID	QD	BID
50	CCI			
150				
300				
600				

Based on the preliminary population pharmacokinetic model, average daily DGAT2 inhibition based on in vitro potency (CCI) was projected to be approximately CCI %, CCI %, CCI % CCI % at doses of 25, 75, 150 and 300 mg administered BID, respectively, and CCI % and CCI % at DGAT2i doses of 150 and 300 mg administered QD.

Administration of DGAT2i 300 mg BID and ACCi 15 mg BID alone and when coadministered over 6 weeks in participants with NAFLD, a placebo-adjusted LS mean reduction in liver fat of ≥40% was observed in all arms. In addition, on average, serum triglyceride increases observed with ACCi alone were mitigated by coadministration with DGAT2i. It is anticipated that via coadministration of DGAT2i + ACCi, hepatic lipid metabolism will be modulated in distinct and complementary ways, potentially resulting in

CCI efficacy than DGAT2i administered alone. As such, this study also includes an evaluation of 2 dose group combinations of DGAT2i and ACCi in order to assess impact on liver histology compared to DGAT2i alone.

DGAT2i 300 mg BID + ACCi 10 mg BID was selected as the high dose combination for the current study. This high dose combination contains the same DGAT2i dose assessed in Study C3711001 (DGAT2i 300 mg BID + ACCi 15 mg BID) though a slightly lower ACCi dose is proposed in this study acknowledging that while mitigation of ACCi-induced effect on serum triglycerides with coadministration of DGAT2i was seen, on average, this response had a range of up to 28% increase in serum triglycerides (ie, upper 90% CI = 27.99% for placebo-adjusted change from baseline for DGAT2i + ACCi) in Study C3711001. The low dose combination chosen is DGAT2i 150 mg BID + ACCi 5 mg BID, half of the high dose combination for each component. However, with both DGAT2i + ACCi dose-levels, the DGAT2i to ACCi dose ratio is maintained at 30:1 (ie, 600:20 and 300:10). The doses of ACCi selected (5 mg BID and 10 mg BID) for coadministration with DGAT2i also align with observed data from Study C1171002 where administration of 2 mg QD of ACCi alone resulted in placebo-like effect, and ACCi doses of ≥10 mg QD resulted in pharmacological evidence of perturbation with clear evidence of dose-related reduction in liver fat, ALT, AST, as well as markers of apoptotic activity (CK18-M30 and CK18-M65). ACCi doses CCI are not proposed in the current study given the CCI linkage between changes in liver fat, ALT, AST, and apoptotic markers and improvements on histological endpoints assessed via liver biopsy. CCI , a BID dosing regimen was selected to match the dosing instructions for the DGAT2i BID arms.

DGAT2i and ACCi doses selected have been demonstrated to be safe and well-tolerated in previous clinical studies and are supported by the CCI studies completed in CCI and CCI for each of the agents alone and CCI combination toxicity study in CCI . In the current study, the highest DGAT2i dose (300 mg BID) and ACCi dose (10 mg BID) proposed are CCI (for DGAT2i) and CCI (for ACCi) CCI than the CCI repeated dose evaluated for each agent in previous clinical studies (refer to Section 2.2.2) as well as afford CCI safety margins compared to completed CCI (refer to Section 2.2.1).

The overall selection of doses of DGAT2i and ACCi were also influenced by the aim to evaluate the study objectives using the tablet strengths available (ie, CCI) as efficiently as possible. As proposed, the dose-range planned will necessitate each participant to self-administer 3 tablets/dose, twice-a-day, in order to maintain the double-blind, double-dummy design of the study. To aid compliance by the participants, study intervention will be packaged and dispensed as blister cards (not bottles) with each card permitting 7 days of dosing – refer to Section 6.

4.4. End of Study Definition

End of study is defined as the date of conduct of the very last 2nd Follow-up visit in a participant randomized into this trial, globally.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Male or female participants between the ages of 18 (or the minimum country-specific age of consent if >18) and 75 years, inclusive, at PreQ *and* SCR1;

    - Refer to Appendix 4 for CCI [redacted] for male (Appendix 4.1) and female (Appendix 4.2) participants.

Type of Participant and Disease Characteristics:

2. At PreQ ***and*** SCR1, meet ≥ **2** of the following criteria [*for laboratory parameters*, results must be as assessed by the sponsor-identified central laboratory, with a single repeat permitted to assess eligibility, at each of these 2 visits, if needed] –

    - FPG ≥ 100 mg/dL (5.6 mmol/L), or on pharmacological agents *with explicit purpose* of improving glycemic control (refer to Section 6.5.1);
    - Fasting serum HDL-C <40 mg/dL (1 mmol/L) for males and <50 mg/dL (1.3 mmol/L) for females, or on pharmacological agents *with explicit purpose* to increase HDL-C (refer to Section 6.5.2);
    - Fasting serum TG ≥150 mg/dL (1.7 mmol/L), or on pharmacological agents *with explicit purpose* to decrease TG (refer to Section 6.5.2);
    - Seated BP ≥130 / 85 mm Hg, or on pharmacological agents *with explicit purpose* for BP control (refer to Section 6.5.3);
    - Waist circumference ≥40 inches (102 cm) for males and ≥35 inches (89 cm) for females.

3. Meet the following criteria, based on an ***evaluable*** FibroScan® as defined in Section 8.1.2.1 (±AST as assessed by sponsor-identified central laboratory); with a single repeat assessment permitted to assess eligibility, if needed, at each of these 2 visits;

    - At PreQ ***and*** SCR1, FAST™ score ≥0.30, derived using sponsor-provided NASH tool;

      OR

    - At PreQ ***and*** SCR1, meet a combination of –

        - CAP™ ≥280 dB/m **plus**

        - VCTE™ between 8.0 and 20.0 kPa, inclusive;

    - Eligibility using this non-invasive assessment must occur prior to conduct of screening/baseline liver biopsy at SCR2.

4. At SCR2, ***ultrasound-guided*** (and in ***limited cases***, other imaging technique(s) as outlined in Section 8.1.1), percutaneous, liver biopsy meeting the NASH CRN definition[14] as determined by sponsor identified central pathologist(s) as follows –

    - A total NAS score of ≥4 (and up to total score of 8) comprising of steatosis grade ≥1, *plus* inflammation grade of ≥1, *plus* ballooning grade of ≥1;

    - *Along* with fibrosis of F2 or F3;

    NOTE: A ***historical*** biopsy may be accepted if performed ≤12 weeks prior to SCR2 ***and*** tissue slides are accessible to the sponsor-identified central pathologist(s) for determination of eligibility (and to serve as baseline); in such cases,

        - Eligibility based on inclusion criterion 3 at PreQ and SCR1 is *not* required;

        - SCR2 date reflects date of shipment of ***historical*** tissue sample to sponsor-identified central laboratory ***after*** confirmation of eligibility based on assessments performed at PreQ and SCR1 visits;

    - ***In all cases***, date of procedure of the liver biopsy used to determine eligibility (and serve as baseline) must be ≤24 weeks prior to Day 1.

5. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures –

    - *Including* following completion of screening/baseline liver biopsy, participants must confirm willingness to undergo the 2nd biopsy, while in study.

Weight:

6. BMI ≥25.0 kg/m^2 (for sites in Africa, Europe, North/South America) ***or*** ≥22.5 kg/m^2 (for sites in Asia) ***with*** upper limit of 45 kg/m^2 (including rounding to a maximum of 45.1 kg/m^2, calculated using sponsor-provided NASH tool) at PreQ and SCR1 with a single repeat assessment of body weight and/or BMI permitted *on a different day* to assess eligibility, if needed, at each of these 2 visits;

    - In all cases, eligibility must conform to ability to ascertain ***evaluable*** FibroScan® (Section 8.1.2.1) ***and*** conduct of ***percutaneous*** liver biopsy (Section 8.1.1).

7. Body weight must be stable (ie, not vary by ≥5% for at least 12 weeks before SCR1).

Informed Consent:

8. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICDs and in this protocol at PreQ and SCR1;

    - For participants who qualify based on PreQ procedures, at SCR1, evidence of a ***separate*** personally signed and dated informed consent document indicating that the participant has been informed of all pertinent aspects of the main study, is required;

        - Plus, *an additional provision/flexibility* for those participating in Imaging Substudy to offer dedicated consent for this procedure closer (but prior) to Baseline MRI-PDFF *or* at the time of consent obtained at SCR1.

5.2. Exclusion Criteria

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

Medical Conditions:

1. Current significant alcohol consumption at ***either*** PreQ *or* SCR1 defined as any ***one*** of these parameters – with a single repeat assessment of laboratory-related parameters permitted using sponsor-identified central laboratory, to assess eligibility, if needed, at each of these 2 visits:

    - >14 drinks/week (men) and >7 drinks/week (women) where 1 drink = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor;
    - %CDT (carbohydrate deficient transferrin) ≥1.5x ULN;
    - Total score of ≥8 on the AUDIT questionnaire.

2. Evidence of other causes of liver disease at ***either*** PreQ *or* SCR1, including any of the following – with a single repeat assessment of laboratory-related parameters permitted

using sponsor-identified central laboratory, to assess eligibility, if needed, at each of these 2 visits:

- Alcoholic steatohepatitis;
- Compensated and decompensated cirrhosis;
- Active viral hepatitis B – defined by presence of HBsAg;
- Active viral hepatitis C – defined as presence of HCVAb;
    - Those who are cured are eligible so long as there is evidence of SVR for ≥3 years, defined as negative HCV RNA result;
- HIV infection defined as presence of HIV antibody;
- Hepatocellular carcinoma or other types of liver cancer;
- Wilson's disease, defined as ceruloplasmin level <0.1 g/L;
- A1AT deficiency, defined as A1AT level <LLN;
- Upper gastrointestinal bleed due to esophageal varices, liver transplant, ***or*** current MELD-Na score[25] >12;
- Histological presence of cirrhosis on screening/baseline liver biopsy.

3. History of pancreatitis, at PreQ.

4. Any condition possibly affecting drug absorption (eg, prior bariatric surgery, gastrectomy, ileal resection) at PreQ;
    - Participants who have undergone cholecystectomy and/or appendectomy are eligible for this study so long as the surgery occurred >6 months prior to PreQ.

5. Diagnosis of T2DM which requires management with >3 medications within 12 weeks prior to SCR1 ***or*** management with excluded agents for glycemic control – refer to Section 6.5.1.

6. Dyslipidemia which requires management with >3 lipid-modifying agents within 12 weeks prior to SCR1 ***or*** use of excluded agents for lipid management –
    - In addition, specific restrictions need to be satisfied **at SCR1** in order to progress
        - Those on gemfibrozil or lovastatin will need to agree to be switched to another agent once deemed eligible (ie, at initiation of Run-In) and for duration of study;
        - Those on statins will be permitted based on review of the total daily dose – refer to Section 6.5.2.

7. At PreQ ***or*** SCR1, those with severe hypertension defined as seated systolic BP ≥180 mmHg, diastolic BP ≥105 mm Hg, **or** both, with a single repeat permitted, if

needed, to assess eligibility at each of these 2 visits; and/or managed with >3 agents to control BP within 12 weeks prior to SCR1 (refer to Section 6.5.3 for acceptable medications) -

- BP must be assessed using a blood pressure cuff size available at individual sites and compatible with the arm circumference of the participant – refer to Section 8.2.4;
- Participants with seated BP ≥160/100 mmHg at PreQ ***or*** SCR1 must use the Run-In period to revise/adjust medications to improve BP control with BP-related randomization criteria met before dosing on Day 1/Visit 5 – refer to Section 5.3.

8. Cardiovascular event within ***12 months*** prior to PreQ; ie:
   - A history of myocardial infarction, stroke, transient ischemic attack or revascularization procedure to prevent any of these events;
   - Recent history of congestive heart failure (NYHA class III or IV) or unstable angina.
9. Recent (within 5 years of PreQ) systemically administered treatments for malignancy including (but not limited to) the use of chemotherapy, radiotherapy, ***or*** immunotherapy;
   - **Or** any other active malignancy (within 3 years of PreQ), except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ.
10. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

11. At SCR1, on any prohibited concomitant medication(s) or those unwilling/unable to switch to permitted concomitant medication(s) – refer to Section 6.5.5.

Prior/Concurrent Clinical Study Experience:

12. Known prior participation in a trial involving DGAT2i ***or*** ACCi (ie, randomized and received at least 1 dose of study intervention, including placebo).

13. Previous administration with an investigational drug or vaccine within 30 days (***or*** as determined by the local requirement) **or** 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer);

    NOTE: administration of *investigational* COVID-19 vaccines (1 dose or 2nd dose of 2-dose regimen) during the screening phase is allowed up to 30 days prior to Visit 4/Baseline; for additional guidance regarding administration of COVID19 vaccines, refer to Section 8.2;

- COVID-19 vaccines authorized under an EUA are ***not*** considered investigational.

Diagnostic Assessments:

14. Results as reported by sponsor-identified central laboratory, at ***either*** PreQ ***or*** SCR1, as below with a single repeat assessment permitted using sponsor-identified central laboratory, to assess eligibility, if needed, at each of these 2 visits:

    - ALT <0.5x ULN ***or*** >5x ULN;
    - AST >5x ULN;
    - ALP >2x ULN;
    - Direct bilirubin >ULN;
    - Total bilirubin >ULN ***except*** when participants has a history of Gilbert syndrome ***where*** total bilirubin >ULN would be eligible for this study provided direct bilirubin level is ≤ULN, and hemoglobin and reticulocyte count are within the reference range of the sponsor-identified central laboratory;

      NOTE: If there is a >50% variability between the PreQ and SCR1 results for ALT, AST, ***or*** alkaline phosphatase ***or*** total bilirubin is >ULN, these LFTs must be repeated 1 additional time, ≥2 weeks after SCR1, with the variability between the PreQ and the 1 additional measurement confirmed to be ≤50% for ALT, AST, ***and*** alkaline phosphatase, ***and*** total bilirubin ≤ULN, **and** within the parameters above to confirm eligibility prior to progressing to conduct of liver biopsy at SCR2;

    - HbA1C >9% (75 mmol/mol), as assessed using NGSP certified method and standardized to DCCT assay;
    - Fasting Plasma Glucose >270 mg/dL (15 mmol/L);
    - Fasting serum triglycerides >400 mg/dL (4.5 mmol/L);
    - Platelet count <LLN;
    - INR ≥1.3;
    - Albumin <LLN;
    - eGFR (using CKD-EPI-Cystatin-C) of <30 ml/min/1.73 m^2;
    - A positive urine drug test for illicit drugs (with this 1 assessment ***not*** permitted to be repeated at each visit to confirm eligibility).

15. At PreQ ***or*** SCR1, supine 12-lead ECG demonstrating QTc interval >480 msec ***or*** QRS interval >120 msec;

    - If QTc interval exceeds 480 msec or QRS interval exceed 120 msec, the 12-lead ECG should be repeated ***twice*** (on the same ***or*** different day) and the ***average of three*** QTc / QRS intervals used to determine eligibility;
    - ***NOTE***: if ***uncorrected*** QT interval is >480 msec, this interval must be rate-corrected using the Fridericia method, with the resulting QTcF used for decision making and reporting.

Other Exclusions:

16. Participants meeting criteria for contraindication to undergoing imaging assessments at ***either*** PreQ ***or*** SCR1;

    - Active placement of medical devices in/on thoracic cavity – such as pacemakers, defibrillators [as these interfere with use of FibroScan® and MRI];
    - ***In addition***, for participants in the Imaging Substudy, history/evidence of any of the following –
        - Contraindication to MRI such as ferric implant;
        - History of severe claustrophobia impacting ability to perform MRI during the study ***even despite*** mild sedation/treatment with an anxiolytic;
        - Inability to lie still within the environment of the MRI scanner or maintain a breath hold for the required period to acquire images ***even despite*** mild sedation/treatment with an anxiolytic;
    - Inability to fit inside the site-specific MRI machine and its' respective bore size to permit acquisition of an ***evaluable*** MRI – refer to Section 8.1.2.2.

17. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.3. Randomization Criteria

A computer-generated randomization code using the method of random permuted blocks will be utilized to randomize participants equally balanced across the 9 study interventions (Original Protocol) or the 7 study interventions (Protocol Amendment 1) on **Day 1/Visit 5** prior to the first dose of the double-blind, double-dummy study intervention provided participants satisfy ***all*** the following criteria:

- Eligibility criteria outlined in Section 5.1 and Section 5.2;
    - *Including* reconfirming that participants are willingness to undergo the 2nd biopsy, while in the study;

- A negative urine drug test for illicit drugs for sample collected at Visit 4/Baseline, as reported by sponsor-identified central laboratory;
- Fasting (≥8 hours overnight, with water permitted) serum triglyceride result of ≤400 mg/dL (4.5 mmol/L), for sample collected at Visit 4/Baseline, as reported by sponsor-identified central laboratory
    - A single repeat assessment permitted using sponsor-identified central laboratory, though results of this repeat, when done, must be available ***ahead*** of randomization;
- Fasting (≥8 hours overnight, with water permitted) plasma glucose result of ≤270 mg/dL (15 mmol/L), for sample collected at Visit 4/Baseline, as reported by sponsor-identified central laboratory
    - A single repeat assessment permitted using sponsor-identified central laboratory, though results of this repeat, when done, must be available ***ahead*** of randomization;
- ***In females,*** a negative serum pregnancy test result at Visit 4/Baseline, as reported by sponsor-identified central laboratory;
    - *Plus*, in females of childbearing potential, urine pregnancy test on Day 1/Visit 5, as reported on-site using supplies offered by sponsor-identified central laboratory, are negative for pregnancy – refer to Section 8.2.6;
- ***In those with hypertension***, BP controlled via adjustment of concomitant medications for BP control during the Run-In period with seated BP on Day 1/Visit 5 of <160/100 mmHg;
- Noted to be ≥90% and ≤110% compliant **with doses administered** (based on tablet count) with the single-blind placebo administered from Visit 4/Baseline to *1 day before* Day 1/Visit 5, inclusive – refer to Section 6.4;
- Total score of <8 on the AUDIT questionnaire, as assessed on Day 1/Visit 5.

Study will employ approximately equal stratification across F2 vs F3 stages of fibrosis on screening/baseline liver biopsy. In addition, attempts will be made to balance randomization across the study intervention arms in the Imaging Substudy (ie, MRI-PDFF).

5.4. Lifestyle Considerations

After confirmation of eligibility across PreQ, SCR1, and SCR2, **at Visit 3/Run-In** (conducted either via telephone contact or as an on-site visit), participants will be instructed to maintain the guidelines described below for the duration of their participation in the study. These guidelines must be reiterated on Day 1/Visit 5.

5.4.1. Contraception

The investigator or his or her designee, in consultation with ***the participant of childbearing potential***, will confirm that the participant has selected an appropriate method of contraception for the individual participant from the permitted list of contraception methods (see Appendix 4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA-Table A1, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4.2. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) for ≥**8 hour**s prior to any blood sample collections for clinical laboratory tests, and the predose PK- and exploratory biomarker-related collections;
    - Water may be consumed as desired (ad libitum);
- Participants must abstain from all food and drink (though water is permitted) for ≥**4 hour**s prior to –
    - Conduct of the FibroScan® assessment
    - Any MRI-PDFF assessment (if participating in Imaging Substudy)
- Blinded study intervention must be administered twice-a-day with –
    - Morning dose at approximately 08:00 AM (±2 hours), local time with breakfast/meal
    - Second dose, at approximately ≥8 and ≤12 hours after the morning dose, with the evening meal;
- At scheduled outpatient visits to the site, in the morning, from Visit 4/Baseline through Week 48/Visit 19, participants must be instructed to arrive without having consumed the morning meal/breakfast and without taking the morning dose of the study intervention *and* concomitant medications for management of glycemic control (Section 6.5.1), lipid control (Section 6.5.2), and blood pressure (Section 6.5.3);
    - At Visit 4/Baseline through Week 48/Visit 19, inclusive, following completion of *all* predose procedures, the morning meal will be consumed with above-mentioned medications at the site;

- The morning meal during site visits will be *either* provided by the site, ***or*** the participant provided a voucher [or similar] by the site to purchase the meal before arriving at the site for each visit.

- Participants will be counseled on appropriate dietary and lifestyle guidelines, at Visit 3/Run-In (conducted either via telephone contact ***or*** an on-site visit) ***and*** again at the on-site visit on Day 1/Visit 5:

  - Counseling on dietary guidelines should be individualized in accordance with local medical standards of care for these participants and appropriate for the concomitant medical condition(s) of each participant;

  - Participants will be asked to maintain these guidelines throughout the study (ie, up to the 1st Follow-up/Visit 20).

5.4.3. Alcohol, Caffeine, and Tobacco

- Intake of alcohol is permitted in moderation – refer to exclusion criterion 1 in Section 5.2 for limits on amount of alcohol consumption;

- Consumption of caffeinated drinks and nicotine-containing products is permitted during participation in the study; however –

  - There may be a need for brief interruption while at the site and/or imaging facility, depending on local policy;

  - Consumption is ***prohibited*** for at least 1 hour prior to any vital sign measurement.

5.4.4. Activity

Participants will **not** be permitted to engage in physically strenuous exercise (for example: heavy lifting, weight training, calisthenics, and aerobics) –

- Within **48 hours** *before* each blood sample collection for clinical laboratory tests for the duration of participation in the study;

- Within **48 hours** *after* completion of the liver biopsy procedure

- Physical activity at an individual participant's normal pace is permitted.

5.4.5. Outpatient Visits to Site

- Each outpatient visit to the site (or Imaging/Radiology facility) is envisioned to occur *with the participant arriving at the site* between approximately 6 AM and 10 AM with each visit lasting approximately 2 hours;

- ***At selected visits***, to permit collection of post dose blood samples for PK, participants may ***either*** extend their stay on-site after dosing ***or*** leave and return later ***the same day*** – refer to Section 8.5 for details.

5.4.6. Outpatient Visits to Imaging/Radiology Facility

- Ultrasound-guided percutaneous liver biopsy of the ***right lobe***, should be performed, following ≥4-hour fast, by trained, medically-qualified investigator – refer to Section 8.1.1 for additional details.

- Assessment via FibroScan®, (in the entire study population), will occur either at the site **or** the imaging facility, depending on where the FibroScan® device is located;

  - However, the location of the device must be kept consistent at individual sites throughout study execution;

  - Assessment to occur at the same time of day (±2 hours) relative to FibroScan® assessment completed at PreQ, ***as much as practically possible*** – refer to Section 8.1.2.1 for additional details.

- Assessment of MRI-PDFF (in the Imaging Substudy population), to occur at the same time of day (±2 hours) relative to Baseline MRI-PDFF completed between Visit 4/Baseline and prior to 1st dose in Day 1/Visit 5, ***as much as practically possible***; refer to Section 8.1.2.2 for additional details.

5.5. 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/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and any SAE.

The ***limited*** participants who screen failed, under the Original Protocol exclusively related to the inclusion criterion #3, inclusion criterion #4, and/or inclusion criterion #6, can be re-screened after Health Authority (where applicable) and IRB/EC approvals of Protocol Amendment 1 – if the amended eligibility criteria can be met. ***In addition***, in ***rare*** cases, participants may be re-screened; however, this is permitted ***only*** when, due to ***logistical/administrative constraints***, the maximum period between PreQ and Day 1/Visit 5, of **16 weeks**, is exceeded;

- ***All*** such cases must be reviewed with a member of the sponsor's Clinical team ***before*** the given participant is re-consented;

- All PreQ ***and*** SCR1 procedures must be repeated under a ***new*** 8-digit SSID number;

- Participants must be deemed to meet all the eligibility criteria including histological assessment of NASH with F2 or F3 fibrosis on SCR2 liver biopsy, as assessed by sponsor-identified central pathologist(s).

6. STUDY INTERVENTION

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

For the purposes of this protocol, **study intervention** refers to ***all*** of the following:

- Placebo matching DGAT2i;
- Placebo matching ACCi;
- DGAT2i;
- ACCi.

6.1. Study Intervention(s) Administered

The following tablet strengths will be provided centrally by the sponsor for use as study intervention:

- For DGAT2i – CCI [redacted] PF-06865571 tablets and matching placebo;
- For ACCi – CCI [redacted] PF-05221304 tablets and matching placebo.

The study intervention above, will be packaged together in blinded blister cards, according to the treatment arms as noted in Table 3, and will be dispensed by the IRT system in sufficient quantities to enable dosing during the intervals between visits outlined in the SoA-Table A1. One extra blister card will be dispensed at *each* dispensation visit to support the flexibility provided by the visit windows. Each blinded blister card supports oral dosing for 7 days and will be labeled according to individual country regulatory requirements. Across the 9 (Original Protocol) or 7 (Protocol Amendment 1) treatment arms, double-blind, double-dummy administration of study intervention will be maintained as outlined in Table 3. Each dose will consist of 3 tablets, ie, 2 large tablets (DGAT2i/matching placebo) and 1 small tablet (ACCi/matching placebo).

Table 3. Double-blind, Double-dummy Regimens in Study C2541013

Regimen		Dose	DGAT2i				ACCi		
Tablet strength (mg)			Placebo/0	CCI			Placebo/0	CCI	
A	Placebo	AM	2	-	-	-	1	-	-
		PM	2	-	-	-	1	-	-
B	DGAT2i 25 mg BID	AM	1	1	-	-	1	-	-
		PM	1	1	-	-	1	-	-

Table 3. Double-blind, Double-dummy Regimens in Study C2541013

Regimen		Dose	DGAT2i				ACCi		
Tablet strength (mg)			Placebo/0	CCI			Placebo/0	CCI	
C	DGAT2i 75 mg BID	AM	-	1	1	-	1	-	-
		PM	-	1	1	-	1	-	-
D	DGAT2i 150 mg BID	AM	1	-	-	1	1	-	-
		PM	1	-	-	1	1	-	-
E	DGAT2i 300 mg BID	AM	-	-	-	2	1	-	-
		PM		-	-	2	1	-	-
F[a]	DGAT2i 150 mg QD	AM	1	-	-	1	1	-	-
		PM	2	-	-		1	-	-
G[b]	DGAT2i 300 mg QD	AM	-	-	-	2	1	-	-
		PM	2	-	-		1	-	-
H	DGAT2i (150 mg BID) + ACCi (5 mg BID)	AM	1	-	-	1	-	1	-
		PM	1	-	-	1	-	1	-
I	DGAT2i (300 mg BID) + ACCi (10 mg BID)	AM	-	-	-	2	-	-	1
		PM	-	-	-	2	-	-	1

a. Participants randomized to Regimen F as part of the Original Protocol will be switched to Regimen C at their next on-site visit, ***and*** new randomization to Regimen F will cease, ***after*** Health Authority (where applicable) and IRB/EC approvals of Protocol Amendment 1 – with the double-blind, double-dummy design maintained;
b. Participants randomized to Regimen G as part of the Original Protocol will be switched to Regimen D at their next on-site visit, ***and*** new randomization to Regimen G will cease, ***after*** Health Authority (where applicable) and IRB/EC approvals of Protocol Amendment 1 – with the double-blind, double-dummy design maintained

6.1.1. Administration

Participants will either self-administer on-site (during scheduled visits) or at home with meals – twice-a-day as outlined in Section 5.4.2. Participants will swallow the study intervention whole and will not manipulate or chew the study intervention prior to swallowing. And each day, participants will be instructed to consume orally, the 3 tablets with the morning meal and 3 tablets with the evening meal.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions 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 authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue

options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. Site staff will instruct participants on the proper storage requirements for take-home study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record. All study intervention that is taken home by the participant, both used and unused, must be returned to the investigator by the participant. Returned study intervention must not be redispensed to the participants.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

A qualified staff member will dispense the study intervention using the IRT system via unique container numbers on the blister cards provided, in quantities appropriate according to the SoA-Table A1. A second staff member will verify the dispensing.

The participant should be instructed to maintain the product in the blister cards provided throughout the course of dosing and return all blister cards, both used and unused to the site at the next on-site study visit.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Approximately 350 participants will be randomized in a balanced ratio to receive either double-blind, double-dummy placebo, 1 of up to 6 doses/dosing regimens of DGAT2i alone, ***or*** 1 of 2 dose-levels of DGAT2i + ACCi. A computer-generated randomization code using

the method of random permuted blocks will be utilized to assign participants to 1 of the 9 (Original Protocol) or 7 (Protocol Amendment 1) study interventions on Day 1/Visit 5. Participants randomized under the Original Protocol will remain randomized under Protocol Amendment 1, and will retain their original randomization number – refer to Table 3 for details on management of the double-blinded treatment assignment between Original and Amendment 1 of this protocol.

Allocation of participants to treatment groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the unique 8-digit participant number. The site personnel will then be provided with a treatment assignment, randomization number, and DU or container number(s) from the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number(s) assigned. The confirmation report must be stored in the site's files.

The study intervention will be dispensed at the study visits summarized in the SoA-Table A1; with returned study intervention ***not*** redispensed to the participants.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.3.2. Breaking the Blind

The blind should ***only*** be broken in emergency situations for reasons of participant safety ***and*** when knowing the specific study intervention that the participant received alters the course of medical management.

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

6.4. Study Intervention Compliance

Compliance with study intervention will be assessed at each on-site visit starting on Day 1/Visit 5 and continuing till Week 48/Visit 19 - refer to SoA-Table A1. Compliance (as assessed by counting blister packs and/or tablets) will be defined as self-administration, by the participants, of:

- Baseline period (ie, Visit 4 to 1 day prior to Visit 5): ≥90% and ≤110% compliance with single-blind, study intervention – based on **number of doses** administered for the *specific* duration of administration; *for example*, to ***remain qualified*** for randomization –

- ***If*** duration of dosing was 10 days, participant can miss a maximum of 2 **doses** (***or*** take a maximum of 2 extra **doses**)
- ***If*** duration of dosing was 18 days, participant can miss a maximum of 3 **doses** (***or*** take a maximum of 3 extra **doses**)

- Day 1/Visit 5 to last day of dosing ***or*** Week 48/Visit 19): ≥80% compliance with self-administration of the study intervention is expected
    - Investigators must closely monitor non-compliant participants in order to enhance participants' adherence to the study intervention;
        - ***Post randomization***, at each dispensation visit (refer to SoA-Table A1), participants who are <80% compliant must be re-educated on the importance of daily self-administration of study intervention;
            - *Overall aim*: maintain ≥80% compliance over the duration of dosing with double-blind, double-dummy study intervention.

6.5. Concomitant Therapy

All concomitant medications taken during the study must be recorded with indication of use. In addition, agents used for glycemic control, lipid control, and blood pressure control, daily dose, and start and stop dates of administration must be captured. All participants must be questioned about concomitant medication at each outpatient visit to the site.

Medications started before **Day 1/Visit 5** will be documented as prior medications. Medications started after dosing of double-blind, double-dummy study intervention on Day 1/Visit 5 and until the 2nd Follow-up/Visit 21, inclusive, will be documented as concomitant medications.

Given the duration of the dosing phase in this study (ie, up to 48 weeks), it is likely that changes in background medications will be needed as part of standard-of-care to manage concomitant medical conditions. For ***three*** specific category of medications – ie, those for glycemic control, lipid control, and BP control – guidance offered herein is requested to be considered when determining how best to maintain control.

6.5.1. Medication for Glycemic Control

Participants are permitted to be on stable doses of up to a ***maximum of 3 agents for glycemic control***, for **≥12 weeks prior to SCR1** and until 1st on-site Follow-up/Visit 20, across the country-specific approved classes of agents for glycemic control (eg, biguanides, DPPIV inhibitors, SGLT2 inhibitors, sulphonylureas, α-glucosidase inhibitors, meglitinide analogues);

- Those on thiazolidinediones/PPARγ (eg, pioglitazone) must be on a stable dose for **≥24 weeks** before SCR1;

- Those on metformin at doses >1 gm/day will need to agree to decrease the dose by one-third or one-half (guided by available tablet strengths) starting at an on-site Visit 3/Run-In conducted ***after*** confirmation of eligibility on SCR2 liver biopsy, with upward adjustment in metformin dose permitted post randomization based on FPG results – refer to Appendix 10;
    - Including once double-blind, double-dummy study intervention is stopped;
- Those on insulin must be on stable doses for **≥12 weeks** before SCR1;
    - Short term use of sliding scale insulin to manage glycemic control during a concomitant acute medical condition is acceptable so long as participant is medically stable at SCR1;
- Those on GLP1r agonists must be on stable doses for **≥12 weeks** before SCR1.

In order to ensure appropriate glycemic control, per local/in-country standard-of-care, and considering the duration of dosing with study intervention (ie, 48 weeks), it may be necessary to adjust the dose(s) of agents for glycemic control post randomization – refer to Appendix 10 for sponsor-suggested guidance.

6.5.2. Lipid-modifying Medications

Participants are permitted to be on stable doses of up to a ***maximum of 3 lipid-modifying oral agents***, for ≥12 weeks **prior to SCR1** and until the 1st on-site Follow-up/Visit 20, across the country-specific, approved classes of agents including the following:

- Those on *selected* statins which are BCRP substrates will only be permitted if on:
    - Rosuvastatin doses up to 10 mg/day;
    - Atorvastatin doses up to 40 mg/day;
    - Simvastatin or Fluvastatin doses up to half-maximum in-country approved dose;

    NOTE: pravastatin and pitavastatin are permitted at doses up to the maximum approved, in-country dose;
- Bile acid sequestrants such as cholestyramine, colestipol, as well as colesevalam;
- Fibric acid derivatives such as fenofibrate, bezafibrate, pemafibrate;
- Nicotinic acid/niacin;
- Ezetimibe;

- Also permitted are over-the-counter/non-prescription supplements known to improve lipid control – such as omega-3 fatty acid, eicosapentaenoic acid.

NOTE: participants requiring use of parenterally administered PCSK9 inhibitors are ***not*** permitted in this study; these agents CCI with the ability to assess effect of DGAT2i and DGAT2i + ACCi on CCI .

The use of CCI permitted starting at Visit 3/Run-In and until the 1 on-site Follow-up/Visit 20;

- Participants on either of these agents, *at SCR1*, will need to agree to be switched to another acceptable agent **starting at** an on-site **Visit 3/Run-In** conducted ***after*** confirmation of eligibility on SCR2 liver biopsy with stable dose of the acceptable agent achieved for ≥ **6 weeks** before Day 1/Visit 5, in order to continue to randomization in this study;

- In the case of CCI , the intent would to be to switch to another statin at an equivalent dose for effect on LDL-C, as outlined below[26] –

Level of Intensity	**High**	**Moderate**	**Low**
LDL-C lowering	≥50%	30% - 49%	<30%
CCI **daily dose**	Not available	40 mg	20 mg
Equivalent daily dose (in mg) of another permitted statin in C2541013, see above		CCI	

In order to ensure appropriate management of the identified adverse drug reaction of elevated fasting serum triglycerides, it may be necessary to adjust the dose(s) of agents for lipid control post randomization – refer to Appendix 11 for sponsor-suggested guidance.

6.5.3. Medications for Controlling Blood Pressure

Across the many classes of agents for management of hypertension, participants are permitted to be on stable doses of up to a ***maximum of 3 agents*** for BP control, for **≥12 weeks prior to SCR1** and until the 1st on-site follow-up/Visit 20;

- Starting at the on-site Visit 3/Run-In, doses of medications can be increased and additional medications can be added to a maximum of 3 in order to control BP and meet criteria needed to progress to randomization - refer to Section 5.2 (exclusion criterion 7) and Section 5.3.

6.5.4. Other Acceptable Concomitant Medications

As much as possible, participants on the following list of medications ***must be*** on stable doses [ie, **≥12 weeks prior to SCR1** and until the 1st on-site Follow-up/Visit 20]

- Use of multi-vitamins is permitted though those on **Vitamin E** must be on stable dose for ***≥24 weeks*** before SCR1;
- Use of aspirin at doses of ≤325 mg/day;
- Use of oral agents that alter stomach pH – eg, antacids, histamine-2 receptor antagonists, proton-pump inhibitors;
- Use of inhaled and topical corticosteroids:
    - *NOTE*: Intercurrent treatment with systemic steroids, during participation in the study, may be permitted if treatment does/will ***not exceed 14 days***;
- Thyroid replacement therapy;
- Postmenopausal hormone therapy;
- Antipsychotic medications such as olanzapine, risperidone;
- Antidepressant medications such as tricyclic agents, selective serotonin reuptake inhibitors and serotonin/norepinephrine reuptake inhibitors;
- Selected (herbal) supplements (***or*** approved agents), below, in countries where they are part of standard of care to lower LFTs *(based on limited/weak scientific evidence)* –
    - Glutathione;
    - Glycyrrhizic acid;
    - Polyene phosphatidylcholine;
    - Silymarin;
    - Ursodeoxycholic acid;
    - For additional guidance, ***for sites in*** [CCI] ***only***, refer to Appendix 8.
- Chronic ***and*** intermittent use of NSAIDs (such as ibuprofen, ketoprofen, diclofenac, naproxen, indomethacin, meloxicam; and celecoxib) is permitted;
- *Intermittent* use of acetaminophen/paracetamol at doses up to 2 grams per day (for example: for short-term pain management) is deemed acceptable;
- Vaccines, as per local country/regional practice for population enrolled – including influenza vaccine, COVID-19 vaccine; for additional guidance regarding administration of COVID-19 vaccines, refer to Section 8.2.

6.5.5. Prohibited Medications

Across the agents use for glycemic control, lipid-modification, and BP control, certain medications are not permitted – refer to above Section 6.5.1 to Section 6.5.3.

Also, use of drugs historically associated with fatty liver are prohibited within **any ≥4 weeks interval** in the previous 12-months prior to SCR1:

- *Examples* include: exemestane, amiodarone, methotrexate, systemic glucocorticoids (such as prednisone, dexamethasone, triamcinolone, budesonide, betamethasone), anabolic steroids, tetracyclines, tamoxifen, estrogens at doses greater than those used for hormone replacement, valproic acid, other known hepatotoxins;

In addition, the use of the following medications **within 12 weeks prior to** SCR1 **or** likely to need these, based on prior medical/medication use history, at any time until 1st on-site Follow-up/Visit 20 must **not** participate in this study –

- *Chronic use* of immunosuppressants such as cyclosporine, tacrolimus, TNF-alpha inhibitors (eg, etanercept, infliximab, adalimumab), IL-6 receptor antagonists (eg, tocilizumab, sarilumab), JAK inhibitors (eg, tofacitinib);
- Pharmacological agents with *approved indication* for weight loss such as orlistat and sibutramine;
- Over-the-counter appetite- simulant or appetite- suppressant, as advertised;
- CCI with CCI;
- Potent inducers and inhibitors of CCI (refer to Appendix 8) including but not limited to the following:
  - Inducers – eg, rifampin, phenytoin, carbamazepine, St John's Wort, phenobarbital;
  - Inhibitors – eg, ketoconazole/itraconazole, clarithromycin, many protease inhibitors (NOTE: participants who are HIV positive are not eligible for this study);
- CCI substrates with CCI (eg, CCI);
- Blood thinner(s) – eg, clopidogrel, apixaban, dabigatran, rivaroxaban, edoxaban, fondaparinux, heparin, as well as Vitamin K antagonists (eg, warfarin);
- Clinically significant CCI – eg, cyclosporine, gemfibrozil, rifampin.

For additional guidance, ***for sites in*** CCI ***only***, refer to Appendix 8.

6.5.6. Rescue Medicine

There is no rescue therapy to reverse the AEs (including identified adverse drug reactions) observed with any of the study interventions; standard medical supportive care must be provided to manage the AEs.

Participant with T2DM with ***repeated*** fasting plasma glucose values >270 mg/dL (15 mmol/L) as reported by the sponsor-identified central laboratory, at two sequential visits post randomization, must have background concomitant medications for glycemic control optimized - starting with the dose of metformin (for those on this agent prior to randomization) – refer to Section 6.5.1 and Appendix 10. These assessments can be a combination of two scheduled visits, ***or*** one scheduled visit followed by an unplanned visit to confirm the elevated result.

CCI [redacted], guidance to investigators is offered (refer to Appendix 11 and Appendix 12) with reversal of effect towards baseline expected/observed in previous studies with CCI [redacted] upon discontinuation of study intervention.

6.6. Dose Modification

Dose of double-blind, double-dummy study intervention in *individual* participants in this study is ***not*** permitted to be modified.

Beyond the strategic decision by the sponsor, via Protocol Amendment 1, related to the 2 QD dosing regimens of DGAT2i alone, the decision to pause *or* stop dosing at a study-level, for 1 or more other active dose(s) of DGAT2i or DGAT2i + ACCi may be considered based on recommendation from the E-DMC according to their review of unblinded, study-level emerging, *observed* safety data – refer to Section 9.6.

6.7. Intervention After the End of the Study

This is the first study to evaluate the efficacy of DGAT2i and DGAT2i + ACCi. As such, 8 active arms (Original Protocol or 6 (Protocol Amendment 1) are being included, to enable identification of efficacious dose(s) upon its' completion (not at start of study). Hence, CCI [redacted] to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include participants who meet preidentified thresholds for identified adverse drug reactions with ACCi – refer to Appendix 11 and Appendix 12, as well as other adverse events based on medical judgment, or some other (administrative) reason.

Note that discontinuation of study intervention does ***not*** represent withdrawal from the study. Participants can continue in the study ***and*** complete all scheduled visits, while off study intervention. If study intervention is definitively discontinued, the participant will remain in

the study to be evaluated for all activities – see the SoA-Table A1 and SoA-Table A2 for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- Discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the participant to comply with the protocol-required schedule of study visits or procedures at a given study site.

In this study, any participant who discontinues participation ***after the PreQ visit but prior to randomization and administration of the 1st dose of double-blind, double-dummy study intervention*** will have no additional procedures completed.

The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

As soon as practically possible ***after*** the decision to withdraw from the study, an on-site visit should be considered –

- Participants should be questioned regarding their reason for withdrawal;
- See the SoA-Table A1 and SoA-Table A2 for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent - refer to Section 7.2.1 for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

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

The following actions must be taken if a participant fails to return to the site 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 or not 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, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain signed and dated ICDs before performing any study-specific procedures at PreQ. ***In addition***, a separate signed/dated ICD must be obtained before performing any study-specific procedures at SCR1.

Study procedures and their timing are summarized in the SoA-Table A1 and SoA-Table A2. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA-Table A1 and SoA-Table A2, 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.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study will range from approximately CCI mL to CCI mL, varying by country, and tube sizes available/used across regions participating in this study. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed CCI mL during any period of 60 consecutive days.

8.1. Efficacy Assessments

8.1.1. Conduct of Ultrasound-guided, Percutaneous Liver Biopsy

In this study, ultrasound-guided, percutaneous biopsy of the *right lobe* of the liver will be undertaken *twice*, following a fast of ≥4-hours *plus* ***wherever practically possible*** at the same time of day (±2 hours) –

- *First*, in all participants who were deemed to be eligible based on double-confirmation via non-invasive assessments between PreQ and SCR1, for purposes of determining eligibility based in histological evidence of NASH with F2-F3 fibrosis (and serve as baseline);
    - Participants with historical liver biopsy ≤12 weeks prior to SCR2 need *not* undergo the study-required screening/baseline liver biopsy ***so long as*** mounted, unstained tissue slides are available for review by sponsor-identified central pathologist(s);
- *Second*, for evaluation of treatment response, when any ***one*** of the following criteria are met –
    - At time of decision to stop study intervention if ≥24 weeks post Day 1/Visit 5;
    - At Week 48/Visit 19 while off study intervention but continuing scheduled visits;
    - At Week 48/Visit 19 (within 2-days of last dose of study intervention).

In limited cases due to excessive abdominal girth (ie, waist circumference) of a participant, conduct of percutaneous liver biopsy is permitted using an alternative imaging technique (eg, computed tomography), as per local policy.

Biopsies may be performed at the study site or the participant may be referred to a Radiology/Imaging facility for the procedure to be undertaken by a medically-qualified investigator –

- Participants must be prepared for the procedure to be conducted under sterile conditions, under local anesthesia, with use of oral/intravenous anxiolytic permitted, as needed;
- Biopsy must be performed, *ideally*, using a 16- gauge needle;
    - An 18- gauge needle is acceptable if this is part of standard practice for the investigator(s) performing the liver biopsy;
    - Biopsy needle smaller than 18 gauge must ***not*** be used as it significantly compromises ability to garner acceptable tissue needed for staging/scoring by the sponsor-identified central pathologist(s);
- Progression of the biopsy needle into the liver capsule must occur *while* the participant is instructed to hold his/her breath;
- Length of tissue sample obtained must be ≥1.5 cm, with the sample cut into ≤10 sections, and each sample 4-5 µm in thickness to improve histological grading/scoring;

- Post procedure ultrasound should be performed to evaluate for any immediate post-biopsy bleed;
- Tissue sample obtained will be processed/prepared using standard methodology and managed by the sponsor-identified central laboratory;
- Complete details regarding biopsy acquisition will be provided in a study-specific manual supplied by the sponsor before the initiation of this study.

As part of understanding the disease (NAFLD/NASH) and the study interventions, CCI [redacted] Participants will have the option to opt in to this additional research, unless prohibited by local regulations or EC decision – refer to Section 8.8.1 and Appendix 5 for additional details.

8.1.2. Liver Imaging Assessments

8.1.2.1. Assessment of Liver Fat and Stiffness – using FibroScan®

In this study, assessments of liver fat and stiffness using FibroScan® will occur at scheduled visits outlined in the SoA-Table A1. The results for liver fat (via CAP™) in dB/m and liver stiffness (via VCTE™) in kPa to determine whether an individual participant qualifies at PreQ to progress to Screen 1 will be displayed on the FibroScan® device at the end of each assessment. Acquisition results do not need independent over-reading, but steps to ensure that acquisition was complete and accurate are required – per training to be offered to **at least 2 site staff** (who *may* be sonographers or comparable) by EchoSens ***and*** certified as operators based on this training by EchoSens, at the start of the study. *As much as practically possible*, attempts will be made to ensure each individual participants' assessment is performed by the same site staff throughout the study.

Complete details regarding acquisitions using FibroScan® to assess CAP™ and VCTE™ will be provided in a FibroScan® Manual supplied by the sponsor before initiation of this study. Conduct of assessments of liver fat and stiffness using FibroScan® must yield evaluable data as defined by compliance with the quality control steps outlined in the sponsor-provided FibroScan® Manual. FibroScan® outputs for selected participants at a subset of nominal timepoints will undergo review against sponsor-defined quality control steps by the Sponsor. The summary of numerical results (including quality-related outputs) must be printed and saved by the study site (or imaging facility, as applicable) as part of each participant's source documents. In addition, all images and output reports acquired must be saved by the study site until the conclusion of the study.

8.1.2.2. Assessment of Liver Fat Using MRI-PDFF (Imaging Substudy)

At scheduled visits (refer to the SoA-Table A1), liver fat (via MRI-PDFF) and total liver volume (via MR volume acquisition protocol) will be assessed, at selected sites in North America, ***only***. All other countries participating in this study will ***not*** be part of the Imaging Substudy.

Transportation of the participants to the Imaging facility does ***not*** need to be supervised by the site staff. Each assessment will require the participants to be in a supine position in the confined space of the MRI scanner for approximately 25 minutes with the image acquisition undertaken **following a fast (except water) of ≥4-hours**, and ***as much as practically possible***, at the same time (±2 hours) of the day relative to assessment at Baseline (ie, between Visit 4/Baseline and prior to 1st dose on Day 1/Visit 5).

Across the study sites selected for this sub-study, the sponsor-identified central imaging vendor will train the staff at the imaging facility on the MRI acquisition protocols, on just-in-time review of the acquired images for assessment of images being deemed evaluable, and on transfer (preferably electronically) of the images to the sponsor-identified central imaging vendor for analysis and quantification of liver fat. **Only the staff members at the imaging facility who are trained by the sponsor-identified central imaging vendor are permitted to acquire images in those who consent for this substudy**, however in rare/limited situations, exceptions may be granted with written approval of the sponsor. Complete details on the MRI-PDFF acquisition protocol, determination of quality of images, and transmission of data to sponsor-identified central imaging vendor will be provided in an Imaging Manual provided to the sites prior to the start of the study.

At the selected visits (refer to the SoA-Table A1) when liver fat is assessed via MRI-PDFF, CCI [redacted] may be acquired for exploratory purposes including liver volume, CCI [redacted], and CCI [redacted] and CCI [redacted], if analyzed, will not be included in the clinical study report but will be summarized via a standalone report.

Management of Incidental Findings

An incidental finding is one unknown to the participant that has potential health or reproductive importance, which is discovered unexpectedly in the course of a research study but is unrelated to the purpose and beyond the aims of the study.

The images will be reviewed by a sponsor-identified central review facility. The purpose of this review is to evaluate images for the amount of fat in the liver. Central image review is not a complete medical review of the participant. If, during the central review process, an unexpected observation is identified and this finding could, in the opinion of the central reviewer, have a significant health or reproductive consequence, this finding may be shared with the study sponsor for disclosure to the PI. All follow-up testing and final diagnosis will be left to the discretion of the medical professionals at the site or those with an existing physician-participant relationship. The PI will be responsible for reporting any AEs identified from incidental findings as described in the AE reporting section. Identification of such incidental findings during the central review process should not be expected, and the site maintains responsibility for performing a general safety review of all images as per site protocols.

CCI [redacted]

[redacted] CCI [redacted] data acquired in this study. Any such analyses will not be included in the clinical study report; a separate supplemental report will be written to capture this work, if undertaken.

8.1.3. Patient-Reported Outcomes

All PRO assessments are implemented using sponsor-provided ePRO device and completed by the participants at home, or at an on-site visit, as per the SoA-Table A1 and Table 4.

Table 4. Patient-Reported Outcome Measures Planned in Study C2541013

Measure	Frequency – refer to SoA-Table A1	Number of questions	*Estimated* Completion time	Assessment
NASH-Check	– Visit 4/Baseline – Week 24/Visit 13 – Week 48/ Visit 19	31	8 minutes	On-site
NASH Symptom Diary (abdominal pain, bloating, fatigue, sleep, and daytime sleepiness)	**Once-a-day** for a *14 consecutive day* period - – During the interval between Visit 4/ Baseline and 1-day prior to Day 1/Visit 5 – ***Starting at*** – o Week 12/Visit 10[a] o Week 24/Visit 13[a] o Week 36/Visit 16[a] (T) – ***Prior to*** Week 48/Visit 19[b]	5	2 minutes	At home, *except* when noted as On-site
NASH PGI-S	**Twice** during a *14-day* period - – During the interval between Visit 4/ Baseline and 1-day prior to Day 1/Visit 5 – ***Starting at*** – o Week 12/Visit 10[a] o Week 24/Visit 13[a] o Week 36/Visit 16[a] (T) – ***Prior to*** Week 48/Visit 19[b]	2	3 minutes	
NASH PGI-C	**Once** during a *14-day* period - – ***Starting at*** – o Week 12/Visit 10[a] o Week 24/Visit 13[a] o Week 36/Visit 16[a] (T) – Week 48/Visit 19 – ***On-site***	2		
PROMIS Fatigue Custom 9-Item Version ("Past 7 days" recall)	– Visit 4/Baseline (*completed On-site*) ***Plus,* once** during a *14-day* period - – ***Starting at*** – o Week 12/Visit 10[a] o Week 24/Visit 13[a] o Week 36/Visit 16[a] (T) – Week 48/Visit 19 – ***On-site***	9		

Table 4. Patient-Reported Outcome Measures Planned in Study C2541013

Measure	Frequency – refer to SoA-Table A1	Number of questions	*Estimated* Completion time	Assessment

a. Site staff required to activate the visit confirmation on *site-specific* sponsor-provided ePRO device, as part of these on-site/telephone visits in order to activate participants ability to start completing these data collections on *participant-specific* sponsor-provided device, at home
b. **At Week 46** (ie, 14±4 days prior to the on-site visit for Week 48/Visit 19) site staff ***required*** to activate the visit confirmation on ***site-specific*** sponsor-provided ePRO device in order to activate participants ability to start completing these data collections on ***participant-specific*** sponsor-provided device, at home; ***in addition***, site must call participants 14±4 days prior to Week 48/Visit 19 to remind them to start completing their required assessments

Every effort should be made to have the participant complete all ePRO assessments; though partial completion of ePRO assessments does *not* preclude continuation of the given visits ***or*** participation in the study.

Additional details regarding ePROs will be provided in a study-specific ePRO training manual supplied by the sponsor before initiation of this study.

8.1.3.1. NASH-CHECK

The NASH-CHECK is a NASH-specific health-related quality of life measure that was developed based on qualitative participant input (Appendix 9.1). It consists of 31 items that measure 3 domains: symptoms (11-point NRS), day-to-day activities (5-point VRS), and emotions and lifestyle (4-point VRS), over the past 7 days.

8.1.3.2. NASH Symptom Diary

The NASH Symptom Diary is a daily, self-administered questionnaire that measures symptoms of NASH (Appendix 9.2). This measure was developed by Pfizer based on qualitative participant input as well as review of other data sources (ie, literature and other existing measures). The measure consists of a total of 5 items that ask participants to rate the severity of their abdominal symptoms (pain and bloating [2 items]), fatigue (1 item), sleep disturbance (1 item), and daytime sleepiness (1 item), in the past 24-hours on an 11-point NRS that ranges from 0 to 10.

8.1.3.3. NASH Patient's Global Impression of Severity (PGI-S)

The NASH PGI-S (Appendix 9.3) consist of two items that ask participants to evaluate their severity of abdominal symptoms (abdominal pain or bloating) and fatigue over the past 7 days on a 5-point VRS that ranges from "None" to "Very severe".

The PGI-S is recommended by US-FDA for use as an anchor measure to generate an appropriate threshold that represents meaningful within-participant change in the target population.

8.1.3.4. NASH Patient's Global Impression of Change (PGI-C)

The NASH PGI-C (Appendix 9.4) consist of two items that ask participants to rate the overall change in their severity of abdominal symptoms (abdominal pain or bloating) and fatigue since they started the study on a 5-point VRS that ranges from "Much better" to "Much worse".

The PGI-C is recommended by US-FDA for use as an anchor measure to generate an appropriate threshold that represents meaningful within-participant change in the target population.

8.1.3.5. PROMIS Fatigue Custom 9-Item Version

The PROMIS Fatigue Custom 9-Item Version (Appendix 9.5) is a self-reported measure that assesses a range of symptoms in the past 7 days from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that likely decreases one's ability to execute daily activities and function normally in family or social roles.

The short form consists of 9 items that participants will be asked to rate from 1: "Never" to 5: "Always". A global raw score ranging from 9 to 45 is calculated and can be translated into a T-score (Mean= 50, SD = 10) using the applicable score conversion table provided in the PROMIS User's Manual.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA-Table A1 and SoA-Table A2. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Considering conduct of this study during the ongoing COVID-19 pandemic, the following guidance is offered for participants receiving COVID-19 vaccines which have temporary authorization or full approval, in the participating countries –

Scope	Action	Considerations
Participants *post randomization* who are considering COVID-19 vaccination[a]	COVID-19 vaccine administration(s), where possible, asked to occur *at least 1-week prior* to scheduled on-site visit	• 1-week prior to on-site visit for Study C2541013 to allow for resolution of signs/symptoms post vaccination (and hence limit impact on fasting laboratory tests collected as part of study C2541013) • Lack of ability to follow scheduling guidance will not be viewed as protocol deviations so long as participant's safety was preserved
Participants who report *SARS-COV-2 positive* result (or	Self-isolate at home until • **At least 10 days** since symptoms first appeared **and**	Proposal *not* to re-test and simply self-isolate is in line with guidelines from the CDC in the

Scope	Action	Considerations

have signs and symptoms of COVID-19)[a]	• **At least 24 hours** with no fever without fever-reducing medication **and**
	• Other symptoms of COVID-19 are improving; though loss of taste and smell may persist for weeks or months after recovery and need not delay the end of isolation
	• *Scheduled* study visits should ***not occur*** during this interval
	  • These visits can ***either*** occur -
	  • outside of window (strongly advocated especially for visits post randomization to ensure continued safety monitoring and adequate IP supply)
	  • *or* be skipped (provided the participant's safety is preserved)
		United States of America (as of 07 January 2021)

Participants who report ***SARS-COV-2 positive*** result ***and*** were hospitalized for a short period[a]	For participants with severe illness from COVID-19 (hospital admission *and* need for supplemental oxygen), self-isolation for ***longer than 10 days*** after symptoms first appeared (possibly up to 20 days) – including need to finish period of isolation at home (post hospital discharge) should be considered
	• *Scheduled* study visits should ***not occur*** during this interval
	  • These visits can ***either*** occur -
	  • outside of window (strongly advocated especially for visits post randomization to ensure continued safety monitoring and adequate IP supply)
	  • *or* be skipped (provided the participant's safety is preserved)
		Proposal ***not*** to re-test and simply self-isolate is in line with guidelines from the CDC in the United States of America (as of 07 January 2021)

a. Details regarding administration of vaccine, any concomitant medications, any AEs are to be captured in the study database, per the language in this protocol and study-specific CRF completion guidelines

8.2.1. Physical Examinations

In this study, physical examinations (including participants' height at selected visits) are to be performed at nominal time points specified in the SoA-Table A1.

- A ***complete*** physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.
- A ***brief*** physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Section 8.3.1 to Section 8.3.3.

8.2.1.1. Measurement of Waist Circumference

Waist circumference will be measured at the nominal time points specified in the SoA-Table A1 using a flexible anthropometric tape and ideally, reporting the measurement in centimeters with accuracy to the nearest 0.1 centimeter (or 1/16th inch).

Measurement will be undertaken as follows:

- While participant is in a standing position with arms resting comfortably at the side;
- At the end of a normal expiration (when lungs are at their residual capacity).

And the measurement will consider the following anatomical features as benchmarks:

- Circumference of the narrowest part of the torso as viewed from the anterior aspect **or;**
- If the narrowest part of the torso cannot be identified, the measurement must be made of the smallest horizontal circumference in the area between the ribs and the iliac crest.

8.2.2. Body Weight

In this study, assessment of body weight will occur at the nominal time points specified in the SoA-Table A1 per the following specifications:

- Weight will be recorded using a scale placed on a stable, flat surface in a (semi)-private area;
- Same scale, ***as much as practically possible***, will be used with the scale reporting weight in kilograms or pounds, and accuracy to the **nearest 0.1 kg [or 0.2 pounds]** ie, the device used for this study must be able to distinguish a difference between 68.4 kg and 68.3 kg.
- Measurement must be undertaken ***and*** documented to 1 decimal place;
- At approximately the same time of the day at each nominal time point.

Under standard conditions (eg, participants must wear light clothing with content of their pockets emptied or hospital gown **and not** be wearing shoes or bulky layers of clothing/jackets).

8.2.3. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10 second rhythm strip) should be collected at times specified in the SoA-Table A1 using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) is ***not*** recommended given the potential risk of discrepancies with ECGs acquired using standard limb lead placement.

- All *scheduled* 12-lead ECGs should be performed after the participant has rested quietly for ≥**10-minutes** in a **supine** position;
- ECG values of potential clinical concern are listed in Appendix 7.
  - ***Starting at Visit 4/Baseline***, if a machine-read QTc value is prolonged, as defined in Appendix 7, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTc values are in the acceptable range;
    - Assessment of whether prolonged QTc interval meets criteria as defined in Appendix 7, must assess QTc interval using ***only*** the Fridericia's correction (ie, QTcF) ***either*** as reported by the 12-lead ECG machine *or* QTcF derived using sponsor-provided tool and reported QT and RR intervals.
- In some cases, it may be appropriate to repeat abnormal 12-lead ECGs to rule out improper lead placement as contributing to the ECG abnormality; ***as much as practically, possible,*** it is important that leads be placed in the same positions each time in order to achieve precise ECG recordings.

8.2.4. Vital Signs

In this study, assessment of vital signs (including seated blood pressure, and pulse rate) will occur at the nominal time points specified in the SoA-Table A1 per the following specifications:

- *At the PreQ visit*, the participants' arm circumference should be measured (using a flexible anthropometric tape) at the midpoint of the length of the upper arm and the appropriate cuff selected and used throughout the study to measure BP/pulse rate via an automated device using an oscillometric method (not auscultation):
  - Participants with arm circumference greater than the largest cuff size available at each site are not eligible.
- **Single seated** blood pressure/pulse rate will be measured with the participant's arm supported at the level of the heart, and recorded to the nearest mm Hg, following a rest of ≥ **5-minutes**;

- Same arm (preferably the dominant arm) will be used for blood pressure/pulse rate assessment throughout the study.

8.2.5. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA-Table A2 for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA-Table A2. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within **28 days** after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

See Appendix 6 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

8.2.6. Pregnancy Testing

Pregnancy tests may be urine and/or serum tests but must have a sensitivity of **at least 25 mIU/mL.** Pregnancy tests will be performed in WOCBP at the times listed in the SoA-Table A2 Following a negative pregnancy test result at screening, appropriate contraception must be commenced (or continued) and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.2.7. Alcohol Intake Assessment

In this study, the ***interview-based*** AUDIT questionnaire[18] will be completed by ***medically qualified site staff*** based on responses offered by the participants – at the visits outlined in the SoA-Table A1. Training for the site staff completing this questionnaire will be offered by the sponsor as part of the protocol-specific training ahead of the initiation of the study.

8.2.8. Triggered requirements and Individual Participant stopping rules

8.2.8.1. Potential Cases of Hypertriglyceridemia

In the current study, fasting serum triglycerides as reported by the sponsor-identified central laboratory, with or without any accompanying signs/symptoms, will be assessed versus the threshold outlined in Appendix 11.

Individual participants with *consistently increasing* fasting serum triglycerides over time ultimately reaching the threshold of ≥ 800 mg/dL (9 mmol/L) as outlined in Appendix 11 should stop dosing with study intervention and an AE of hypertriglyceridemia captured.

When considering adjustment of dose(s) of background lipid-modifying agents in order to manage elevating fasting serum triglyceride results, investigators must consider the guidance offered in Section 6.5.2 related to doses of certain lipid-modifying agents ***and*** take action only when it has been established that observed result is not due to lack of compliance with dosing of study intervention and/or background lipid-modifying agents.

8.2.8.2. Potential Cases of Thrombocytopenia

In the current study, platelet count as reported by the sponsor-identified central laboratory, with or without any accompanying signs/symptoms, will be assessed versus the threshold outlined in Appendix 12.

- In participants ***observed*** to have platelet count below the LLN should have an unplanned visit occur ***as soon as practically possible*** to –
  - Inquire about adverse events via open-ended inquiry;
  - Confirm via open-ended inquiry that participant has been following dosing instructions as intended (and outlining in the dosing instructions) *and* that there is no case of medication error;
  - *And* collect blood sample to permit safety-related laboratory assessments included hematology panel assessment by the sponsor-identified central laboratory.

Participants who have been following dosing instructions ***and*** in whom *consistent decline over time* ultimately reaching the threshold of <75,000/mm^3 in platelet count has been observed as outlined in Appendix 12 should stop dosing with study intervention and an AE of thrombocytopenia captured.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention - refer to Section 7.1.

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a ***minimum of 28 calendar days***, except as indicated below, after the last administration of the study intervention or until study completion or withdrawal, whichever is longer.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are recorded on the CRF. AEs and SAEs that begin after obtaining informed consent but before the start of study intervention will be recorded on the Medical History/Current Medical Conditions section of the CRF, not the AE section. AEs and SAEs that begin after the start of study intervention are recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor 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. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
  - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.
  - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until ***at least 28 days*** after the last dose of study intervention.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a

follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death, the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a

CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

CCI [redacted]

In this study, CCI [redacted] are the CCI [redacted]

- Increase in *fasting* CCI [redacted] – refer to Appendix 11 – ideally via double-confirmation provided participant is asymptomatic;
- Reduction in CCI [redacted] – refer to Appendix 12 – ideally via double-confirmation provided participant is asymptomatic.

All CCI [redacted] must be reported as an AE or SAE following the procedures described in Sections 8.3.1 through 8.3.4. An CCI [redacted] is to be recorded as an AE or SAE on the CRF. In addition, an CCI [redacted] that is also an SAE must be reported using the CT SAE Report Form.

8.3.7. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

8.4. Treatment of Overdose

For this study, any dose of DGAT2i greater than CCI mg, ***or*** any dose of ACCi greater than CCI mg, within a 24-hour time period will be considered an overdose.

Sponsor does ***not*** recommend specific treatment for an overdose. However, in the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of study intervention.
3. Obtain a blood sample for PK analysis ***as soon as practically possible***;
4. Document the quantity of the excess doses as well as the duration of the overdose in the CRF.
5. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

In this study, blood samples (approximately **5 mL** each) to provide sufficient [redacted] for pharmacokinetic analysis will be collected into appropriately labeled tubes containing K2-EDTA, at times defined in the SoA-Table A2. The date/time of the blood draw and the date/time of the previous ***two*** doses of double-blind, double-dummy study intervention prior to ***each*** of the blood draws related to PK (both pre- *and* post- dose samples) should be noted in a dosing diary (or similar) by the participants and captured in the eCRF.

- The PK samples must be processed and shipped as indicated in the study-specific laboratory manual provided to the site, prior to initiation of study, to maintain sample integrity:
  - Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation;
  - ***Any*** of the following errors in *scheduled* collection of blood samples for PK (refer to SoA-Table A2) will be captured as protocol deviations even if results are deemed to be evaluable –
    - Predose collection (ie, C_{trough}) obtained post dose;
    - Post dose PK sample *not* collected within collection window following morning dose;
    - PK sample (pre- or post- dose) *not* collected.
- As part of understanding the pharmacokinetics of the study intervention, samples may be used for [redacted]. These data will not be included in the clinical report;
- Samples will be analyzed for DGAT2i and/or ACCi using a validated analytical method in compliance with Pfizer standard operating procedures.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

However, refer to Section 8.2 for details regarding the planned safety-related assessments and Section 8.8 for collections related to exploratory biomarkers, planned in this study.

CCI [redacted]

A CCI [redacted] will be collected into plastic K_2-EDTA tubes, as defined in the SoA-Table A2. CCI [redacted] samples will be analyzed for the purpose of assessing the impact of CCI [redacted]. As part of these analyses, CCI [redacted] Additionally, these samples may also be used for CCI [redacted] Samples will be retained for a period of **up to 3 years after regulatory approval.**

In the event of CCI [redacted], a replacement CCI [redacted] blood sample may be requested from the participant.

See Appendix 5 for information regarding CCI [redacted] research. Details on processes for collection and shipment of these samples can be found in sponsor-identified study-specific central laboratory manual.

The CCI [redacted] must be processed and shipped as indicated in the instructions provided to the investigator site, to maintain sample integrity. Any deviations from the CCI [redacted] steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

As part of further understanding the biological response to study intervention, samples may be used for CCI [redacted]

CCI [redacted] and will not be included in the clinical study report.

CCI [redacted]

A CCI [redacted] will be collected as local regulations and IRBs/ECs allow - as defined in the SoA-Table A2.

CCI [redacted] may be used for research related to the study intervention(s) and NAFLD/NASH. CCI [redacted]

The CCI [redacted] does not require the collection of any further samples.

See Appendix 5 for information regarding CCI [redacted]. Details on processes for collection and shipment of these samples can be found in sponsor-identified study-specific central laboratory manual.

8.8. Biomarkers

Collection of samples for biomarker research is part of this study.

Blood, serum, plasma, and liver biopsy tissue samples for exploratory/tertiary endpoint biomarkers, including NASH-related biomarkers, potential mechanism-related parameters, metabolic parameters, and to aide in understanding the study interventions, will be collected at the nominal time points defined in the SoA-Table A2.

- These samples must be processed and shipped as indicated in the study-specific laboratory manual provided by the sponsor to the site, prior to initiation of study, to maintain sample integrity:
  - Any deviations from the sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, ***must*** be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation;
  - Any ***scheduled*** collection prior to next dose of double-blind, double-dummy study intervention, if undertaken postdose, will be captured as a protocol deviation even if results are deemed evaluable;
- Samples will be analyzed using a validated analytical method (which need ***not*** meet GLP standards, especially for these exploratory endpoints) but in all cases, the method will be in compliance with Pfizer standard operating procedures.

In addition, as part of further understanding the biological response to study intervention, samples may be used for evaluation of other related biomarkers as well as development and validation of bioanalytical methods. These data will be used for internal exploratory purposes and will ***not*** be included in the clinical study report.

CCI [redacted]

CCI [redacted]

See Appendix 5 for information regarding CCI [redacted]. Details on processes for collection and shipment of these samples can be found in sponsor-identified study-specific central laboratory manual.

CCI [redacted]

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

For the primary objective of the study, the primary estimand (**Estimand 1.1**) will use a composite estimand strategy, in participants with biopsy-confirmed NASH and fibrosis, as assessed by the sponsor-identified central pathologist(s), to estimate the treatment effect of DGAT2i doses administered alone and coadministration of DGAT2i + ACCi relative to placebo, and coadministration of DGAT2i + ACCi, relative to DGAT2i alone, in terms of the proportion of 'clinical responders', defined as participants achieving centrally adjudicated: resolution of NASH without worsening of fibrosis or improvement in fibrosis by ≥1 stage without worsening of NASH, or both, at Week 48 and treating all cases of withdrawal from treatment for lack of efficacy or toleration as non-responders. All treatment effect contrasts

will be obtained through fitting the Bayesian dose-response and/or exposure-response models with a logit transformation, or logistic regression models.

A secondary estimand to assess the primary objective will be:

- **Estimand 1.2**: Using a hypothetical estimand strategy, in participants with biopsy-confirmed NASH and fibrosis, as assessed by the sponsor-identified central pathologist(s), estimate the treatment effect of DGAT2i doses administered alone and coadministration of DGAT2i + ACCi relative to placebo, and coadministration of DGAT2i + ACCi, relative to DGAT2i alone, in terms of estimating the proportion of 'clinical responders', defined as participants achieving centrally adjudicated: resolution of NASH without worsening of fibrosis or improvement in fibrosis by ≥1 stage without worsening of NASH, or both, at Week 48, assuming all participants had remained in the trial and received treatment as planned without withdrawal up to 48 Weeks. Endpoint data collected after treatment withdrawal will be censored. All treatment effect contrasts will be obtained through fitting the Bayesian dose-response and/or exposure-response models with a logit transformation, or logistic regression models.

Secondary estimands to assess secondary objectives will be:

- **Estimand 2.1**: Using a composite estimand strategy, in participants with biopsy-confirmed NASH and fibrosis, as assessed by the sponsor-identified central pathologist(s), estimate the treatment effect of DGAT2i doses administered alone and coadministration of DGAT2i + ACCi relative to placebo, and coadministration of DGAT2i + ACCi, relative to DGAT2i alone, in terms of the proportion of 'clinical responders', defined as participants achieving centrally adjudicated resolution of NASH without worsening of fibrosis, at Week 48 and treating all cases of withdrawal from treatment for lack of efficacy or toleration as non-responders. All treatment effect contrasts will be obtained through fitting the Bayesian dose-response and/or exposure-response models with a logit transformation, or logistic regression models.

- **Estimand 2.2**: Using a composite estimand strategy, in participants with biopsy-confirmed NASH and fibrosis, as assessed by the sponsor-identified central pathologist(s), estimate the treatment effect of DGAT2i doses administered alone and coadministration of DGAT2i + ACCi relative to placebo, and coadministration of DGAT2i + ACCi, relative to DGAT2i alone, in terms of the proportion of 'clinical responders', defined as participants achieving centrally adjudicated improvement in fibrosis by ≥1 stage without worsening of NASH, at Week 48 and treating all cases of withdrawal from treatment for lack of efficacy or toleration as non-responders. All treatment effect contrasts will be obtained through fitting the Bayesian dose-response and/or exposure-response models with a logit transformation, or logistic regression models.

- **Estimand 2.3**: Using a composite estimand strategy, in participants with biopsy-confirmed NASH and fibrosis, as assessed by the sponsor-identified central pathologist(s), estimate the treatment effect of DGAT2i doses administered alone and

coadministration of DGAT2i + ACCi relative to placebo, and coadministration of DGAT2i + ACCi, relative to DGAT2i alone, in terms of the proportion of 'clinical responders', defined as participants achieving centrally adjudicated improvement in fibrosis by ≥2 stages without worsening of NASH, or both, at Week 48 and treating all cases of withdrawal from treatment for lack of efficacy or toleration as non-responders. All treatment effect contrasts will be obtained through fitting the Bayesian dose-response and/or exposure-response models with a logit transformation, or logistic regression models.

- **Estimand 2.4**: Using a composite estimand strategy, in participants with biopsy-confirmed NASH and fibrosis, as assessed by the sponsor-identified central pathologist(s), estimate the treatment effect of DGAT2i doses administered alone and coadministration of DGAT2i + ACCi relative to placebo, and coadministration of DGAT2i + ACCi, relative to DGAT2i alone, in terms of the proportion of 'clinical responders', defined as participants achieving centrally adjudicated improvement of ≥2 points on Total NAFLD Activity Score (NAS) at Week 48 and treating all cases of withdrawal from treatment for lack of efficacy or toleration as non-responders. All treatment effect contrasts will be obtained through fitting the Bayesian dose-response and/or exposure-response models with a logit transformation, or logistic regression models.

- **Estimand 2.5**: Using a hypothetical estimand strategy, in participants with biopsy-confirmed NASH and fibrosis, as assessed by the sponsor-identified central pathologist(s), estimate the treatment effect of DGAT2i doses administered alone and coadministration of DGAT2i + ACCi relative to placebo, and coadministration of DGAT2i + ACCi, relative to DGAT2i alone, in terms of the population level average percentage change from baseline in liver fat (assessed via MRI-PDFF) at Week 48, assuming all participants had remained in the trial and received treatment as planned without withdrawal up to 48 weeks. Endpoint data collected after treatment withdrawal will be censored. All treatment effect contrasts will be obtained through fitting the Bayesian dose-response and/or exposure-response models, or ANCOVA models.

9.1.2. Hypothesis Tests

For this study there are no formal hypothesis tests planned.

9.2. Sample Size Determination

The sample size estimation for this study is driven by the characterization of dose response and treatment effect using a Bayesian E_{max} study design and modelling approach, which will utilize weakly informative priors for model parameters and will provide the ability to make more precise comparisons between treatment arms. The sample size calculation is based on the primary efficacy endpoint, the proportion of participants with improvement in fibrosis without worsening of NASH or NASH resolution without worsening of fibrosis, or both improvement in fibrosis and NASH resolution at Week 48.

The DGAT2i ED_{50} for the histological-based primary endpoint has been assumed to be slightly higher than the projected EC_{50} for reduction in liver fat which was estimated from a preliminary population pharmacokinetic model based on previous clinical studies with DGAT2i. Therefore, the DGAT2i ED_{50} was estimated to be approximately 30 mg BID and the placebo responder rate (E_0) was estimated to be 16%. It is estimated that a total sample size of 350 participants (50 randomized participants per arm) will give acceptable probabilities to make decisions about the dose response in a NASH population based on simulation studies. At the theoretical E_{max} of 0.6 (ie, a 60% responder rate), there would be enough precision to show a greater than 24% difference in the primary endpoint responder rate between placebo and the second highest BID dose of DGAT2i (ie, 150 mg BID) with a probability of at least 89%.

In addition, this sample size will provide adequate precision to assess whether DGAT2i + ACCi provides a higher responder rate than DGAT2i monotherapy with a probability of 82% if the true effect size is at least 6%.

9.3. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Patients Analysis Set	Description
Enrolled	All participants who sign the PreQ ICD
Randomly assigned to investigational product	All randomized participants
Evaluable	Defined according to the Full Analysis Set: All randomized participants who take at least 1 dose of investigational product who have provided baseline data for the primary endpoint (i.e. baseline biopsy data). Participants will be analyzed according to the treatment group they are randomized to. • The only exception to this is for participants randomized before Protocol Amendment 1 is enacted who are randomized to either of the 2 QD dosing regimens of DGAT2i alone, who switch to the corresponding BID dosing regimen of DGAT2i alone, and will be analyzed under that treatment group.
Safety	All randomized participants who take at least 1 dose of investigational product. Participants will be analyzed according to the treatment they actually received. • The only exception to this is for participants randomized before Protocol Amendment 1 is enacted who are randomized to either of the 2 QD dosing regimens of DGAT2i alone, who switch to the corresponding BID dosing regimen of DGAT2i alone, and will be analyzed under that treatment group.

Defined Analysis Data Set (at the data level) – endpoint specific	Description
All biopsy-derived endpoints	
Biopsy-based Composite Estimand	If a participant discontinues treatment or from the study due to lack of efficacy or toleration prior to Week 48 or if they do not have Week 48 Biopsy data, they will be considered to be a non-responder.
Biopsy-based Hypothetical Estimand	Any available biopsy data for all participants collected before or at the time of treatment withdrawal will be included in the analysis, even if they have withdrawn from treatment for lack of efficacy or toleration. Endpoint data collected after treatment withdrawal will be censored.
All MRI-PDFF-derived endpoints (in Imaging Substudy)	
MRI-based Hypothetical Estimand	Any available MRI data for all participants collected before or at the time of treatment withdrawal will be included in the analysis, even if they have withdrawn from treatment for lack of efficacy or toleration. Endpoint data collected after treatment withdrawal will be censored.

9.4. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints of the study.

9.4.1. General Considerations

For the assessment of dose-response, the following BID treatment groups (at a minimum) will be included in a Bayesian E_{max} dose-response model:

- Placebo
- DGAT2i 25 mg BID
- DGAT2i 75 mg BID – including those randomized to 150 mg QD – refer to Table 3
- DGAT2i 150 mg BID – including those randomized to 300 mg QD – refer to Table 3
- DGAT2i 300 mg BID

Other treatment groups will be analyzed to assess the comparisons as shown below:

- DGAT2i 150 mg BID + ACCi 5 mg BID vs DGAT2i 150 mg BID
- DGAT2i 300 mg BID + ACCi 10 mg BID vs DGAT2i 300 mg BID

9.4.2. Primary Endpoint(s)

The proportion of participants achieving resolution of NASH without worsening of fibrosis or improvement in fibrosis by ≥1 stage without worsening of NASH, or both, based on assessment by sponsor-identified central pathologist(s) at Week 48 and treating all cases of

withdrawal from treatment for lack of efficacy or toleration as non-responders, will be analyzed by fitting a Bayesian E_{max} dose-response model. This model will be utilized to characterize the dose response across all DGAT2i BID treatment groups, to estimate the proportion of responders (and 95% CI) for each dose studied, and to estimate the placebo-adjusted proportion of responders for each dose (and 95% CI). If an E_{max} dose-response model cannot be fitted to the data, then other models that allow dose response to be estimated will be fitted, ie, linear, log-linear or exponential. No adjustment for multiple comparisons will be made.

The Bayesian estimation of the E_{max} dose-response model uses prior distributions on the placebo response (E_0), dose that produces half maximal drug effect (ED_{50}) and E_{max} parameters. The specification of the E_{max} model and the prior distributions for some of its parameters are based on three meta-analyses of clinical dose response from more than 100 compounds[27,28,29]. The current assumed value for ED_{50} is 30 mg BID, which is based on exposure-response analyses of DGAT2i for liver fat (Section 4.3), utilizing data from previous clinical studies with DGAT2i and assuming a translation to a slighter higher ED_{50} for a histological endpoint. The substantial uncertainty in ED_{50} values was assessed in the meta-analyses of clinical dose response studies[29]. Therefore, based on the meta-analyses, a scaled t-distribution (with 5 degrees of freedom) is planned to be used that is focused on the initial projected ED_{50}=30 mg BID, with a scale parameter of 0.6. A normal prior distribution for the logit of the placebo response centered at logit (0.16) with a prior standard deviation of 2.0 (logistic scale) is planned to be used, which yields a weak diffuse prior distribution for the placebo response. A normal prior distribution for the E_{max} parameter will also be used, centered on the anticipated E_{max} (0.6) on the logistic scale. This prior distribution will also be diffuse on the logistic scale with a prior standard deviation of 2.0.

The comparisons of the proportion of participants achieving resolution of NASH without worsening of fibrosis or improvement in fibrosis by ≥1 stage without worsening of NASH, or both, based on assessment by sponsor-identified central pathologist(s) at Week 48 and treating all cases of withdrawal from treatment for lack of efficacy or toleration as non-responders, for DGAT2i + ACCi BID vs placebo and vs the corresponding DGAT2i BID monotherapy dose will be analyzed using a logistic regression model to estimate the proportion of responders in each treatment group and odds ratio (and corresponding 95% CI) for each treatment comparison.

In order to estimate the hypothetical secondary estimand, the primary endpoint will also be analyzed to assess treatment differences, assuming all participants had remained in the trial and received treatment as planned without withdrawal up to Week 48. All treatment effect contrasts will be obtained through fitting the Bayesian dose-response and/or exposure-response models with a logit transformation, or logistic regression models. This estimand assesses the treatment effect in an alternative, hypothetical setting of adherence to their treatment as planned.

9.4.3. Secondary Endpoint(s)

Binary (responder) endpoints

The proportion of participants achieving resolution of NASH without worsening of fibrosis, based on assessment by sponsor-identified central pathologist(s) at Week 48 and treating all cases of withdrawal from treatment for lack of efficacy or toleration as non-responders, will be analyzed by fitting a Bayesian E_{max} dose-response model. This model will be utilized to characterize the dose response across all BID treatment groups, to estimate the proportion of responders (and 95% CI) for each BID dose studied, and to estimate the placebo-adjusted proportion of responders for each dose (and 95% CI). If the E_{max} dose-response model cannot be fitted to the data, then other models that allow dose response to be estimated will be fitted, ie, linear, log-linear or exponential. No adjustment for multiple comparisons will be made.

Similar analyses will be performed for the following secondary endpoints:

- Proportion of participants with improvement in fibrosis by ≥1 stage without worsening of NASH, based on assessment by sponsor-identified central pathologist(s) at Week 48
- Proportion of participants with improvement in fibrosis by ≥2 stages without worsening of NASH, based on assessment by sponsor-identified central pathologist(s) at Week 48
- Proportion of participants with improvement of ≥2 points on Total NAS, based on assessment by sponsor-identified central pathologist(s) at Week 48

The comparison of the proportion of responders for each of the binary secondary endpoints for DGAT2i + ACCi BID doses vs placebo as well as versus the corresponding DGAT2i BID monotherapy doses will be analyzed an using logistic regression models to estimate the proportion of responders in each treatment group and odds ratio (and corresponding 95% CI) for each treatment comparison. For comparisons of DGAT2i + ACCi BID doses vs corresponding DGAT2i BID monotherapy doses corresponding 50% CI will also be provided. No adjustment for multiple comparisons will be made.

Continuous endpoints

The continuous endpoint, percentage change from baseline in liver fat (assessed via MRI-PDFF) at Week 48, will be analyzed using a Bayesian E_{max} dose-response model for the DGAT2i BID doses.

The comparison of the percentage change from baseline in liver fat (assessed via MRI-PDFF) at Week 48 for DGAT2i + ACCi BID vs placebo and vs the corresponding DGAT2i BID monotherapy dose will be analyzed using an ANCOVA performed on log-transformed relative change from baseline with treatment (where relative change from baseline = post baseline value/baseline value) and baseline fibrosis stage (F2/F3) as factors, and log-transformed baseline liver fat value as a covariate. Estimates of the mean relative changes for each treatment comparison and the corresponding 95% CI will be obtained from the model. The mean relative changes and their CIs will be exponentiated and percent change will then

be determined as follows: Percent change = 100* (Relative Change - 1). For comparisons of DGAT2i + ACCi BID vs the corresponding DGAT2i BID monotherapy dose the corresponding 50% CI will also be provided. No adjustment for multiple comparisons will be made.

Descriptive summaries of the observed values and percent change from baseline in liver fat for each treatment group will also be produced.

9.4.4. Tertiary/Exploratory Endpoint(s)

The following tertiary/exploratory endpoints will be analyzed using similar methods to those planned for other similar secondary endpoints:

- Proportion of participants with worsening of fibrosis by ≥1 stage, on liver biopsy, as assessed by sponsor identified central pathologist(s), at Week 48
- Proportion of participants with worsening of ≥2 points in Total NAS on liver biopsy, as assessed by sponsor identified central pathologist(s), at Week 48

Additional exploratory analyses will be performed on these endpoints if warranted, similar to those described for other secondary binary (responder) endpoints.

9.4.5. Pharmacokinetic Analysis

CCI concentration data for DGAT2i and ACCi (ACCi concentrations for Treatments H and I only – refer to Table 3) will be listed by Cohort.

In addition, as permitted by data and determined by the sponsor, CCI concentrations of DGAT2i and/or ACCi and effect on primary (biopsy), secondary and tertiary endpoints may be characterized CCI The objectives of such an analysis, if conducted, would aim to characterize CCI and explore potential covariates (eg, age, race, gender, and body weight, etc) influencing the observed PK and/or response to DGAT2i and/or ACCi. The CCI and/or CCI analyses, if conducted, will be reported separately from the main clinical study report.

9.4.6. Other Safety Analyses

All safety analyses will be performed on the safety population. These will be presented in tabular and/or graphical format and summarized descriptively and will follow Pfizer standards as appropriate.

The MedDRA will be used to classify all AEs with respect to system organ class and preferred term. Summaries of AEs will include treatment-emergent AEs according to treatment group.

Furthermore, a 3-tier approach will be used to summarize AEs. Tier-1 consists of pre-specified adverse events of interest and will include AEs or collections of AEs related to identified adverse drug reactions in this program related to either DGAT2i or ACCi. Where

available, standard MedDRA queries will be used to pool different AE terms that are related to the Tier-1 AEs. The precise AE terms that will contribute to the Tier-1 endpoints will be determined prior to unblinding. For these events, the percentage of participants with incident AE, the risk difference, its 95% CI, and p-value will be provided. The CI s and p-values are not adjusted for multiplicity and are provided for screening purposes only. Tier-2 AEs are those that are not Tier-1, but are common, occurring in at least 4 participants in any treatment arm. The cut-off of at least 4 events was chosen because the 95% CI for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and so adds little to the interpretation of potentially meaningful differences. For these events, the percentage of participants with incident AE, the risk difference and its 95% CI will be provided. The CIs are for estimation purposes only. Tier-3 AEs are all other AEs (neither Tier-1 nor Tier-2). For Tier-3 AEs, only within-group incidence proportions will be tabulated.

9.4.6.1. Vital Signs Analyses

Changes from baseline in systolic blood pressure, diastolic blood pressure and pulse rate will be summarized by treatment and time. The number (%) of participants with maximum increases from baseline will be tabulated by treatment as defined in the SAP. Numbers and percentages of participants meeting the categorical criteria will be provided and individual values listed in the study report. No formal inferential statistics will be applied to the vital signs data.

9.4.6.2. Electrocardiogram Analyses

Changes from baseline for the ECG parameters QT interval, heart rate, QTcF interval, PR interval, and QRS interval will be summarized by treatment and time. For purposes of reporting study-level results, QTcF interval will be derived using Fridericia's heart rate correction formula applied to databased QT interval, and RR interval. The number (%) of participants with maximum increases from baseline will be tabulated by treatment as defined in the SAP. Numbers and percentages of participants meeting the categorical criteria summarized in Table 5 will be provided and individual values listed in the study report. No formal inferential statistics will be applied to the ECG data.

Table 5. Safety-Related Assessment of QT and QTcF Interval

Degree of Prolongation	QTcF Interval Prolongation (msec)			Uncorrected QT Interval (msec)
	Mild (msec)	Moderate (msec)	Severe (msec)	
Absolute value	>450-480	>480-500	>500	> 500
Increase from baseline		30-60	>60	

9.4.7. Other Analyse(s)

Beyond the objectives, estimands, and endpoints outlined in Section 3, this study will also evaluate the objectives/endpoints summarized in Table 6.

Table 6. Additional Tertiary/Exploratory Objectives and Endpoints

Objectives	Estimands	Endpoints
To evaluate the effect of a range of DGAT2i doses administered alone, and coadministration of DGAT2i + ACCi, compared to placebo, and the coadministration of DGAT2i + ACCi relative to DGAT2i alone, on ***liver fat***		Percent change in liver fat (assessed via MRI-PDFF in Imaging substudy population), over time up to Week 48
To evaluate the effect of a range of DGAT2i doses administered alone, and coadministration of DGAT2i + ACCi, compared to placebo, and the coadministration of DGAT2i + ACCi relative to DGAT2i alone, on ***liver volume,*** CCI [redacted]		Percent change in liver volume, CCI [redacted] (assessed via MRI in Imaging substudy population), over time up to Week 48
To evaluate the effect of a range of DGAT2i doses administered alone, and coadministration of DGAT2i + ACCi, compared to placebo, and the coadministration of DGAT2i + ACCi relative to DGAT2i alone, on ***liver fat***		Percent change from baseline in liver fat as assessed via CAP™ measure by FibroScan®, (entire study population), over time up to Week 48
To evaluate the effect of a range of DGAT2i doses administered alone, and coadministration of DGAT2i + ACCi, compared to placebo, and the coadministration of DGAT2i + ACCi relative to DGAT2i alone, on ***liver stiffness***		Percent change from baseline in liver stiffness (assessed via VCTE™ using FibroScan® (entire study population), over time up to Week 48
To evaluate the effect of a range of DGAT2i doses administered alone, and coadministration of DGAT2i + ACCi, compared to placebo, and the coadministration of DGAT2i + ACCi relative to DGAT2i alone, on ***liver function tests: ALT, AST, ALP, GGT***		Percent change from baseline in ALT, AST, ALP and GGT over time up to Week 48
To evaluate the effect of a range of DGAT2i doses administered alone, and coadministration of DGAT2i + ACCi, compared to placebo, and the coadministration of DGAT2i + ACCi relative to DGAT2i alone, on ***biomarkers of pharmacology and/or disease state – over time***		Percent change from baseline, overtime up to Week 48 in • PCSK9 • CK18-M30 and CK18-M65, • ProC3 and ProC6 • ELF test • hs-CRP
To evaluate the effect on other potentially mechanism-related parameters and metabolic parameters, ***over time***, with a range of DGAT2i doses administered alone, and coadministration of DGAT2i + ACCi, compared to placebo, and the coadministration of DGAT2i + ACCi relative to DGAT2i alone, in all participants in the study		Percent change from baseline, overtime up to Week 48, for: • Potentially mechanism-related parameters Apolipoprotein A1, B (total), B100, B48, C3, E • Metabolic parameters including - – HbA1C – Fasting lipid panel (total cholesterol, direct LDL-C, HDL-C, triglycerides, direct VLDL) – Adiponectin – Body weight
To evaluate the effect of a range of DGAT2i doses administered alone, and coadministration of DGAT2i + ACCi, compared to placebo, and the coadministration of DGAT2i + ACCi relative to DGAT2i alone, on ***parameters of glycemic control in adults with T2DM, only***		Percent change from baseline, over time up to Week 48, in: • HbA1C • FPG • FPI • HOMA-IR
To evaluate the effect of a range of DGAT2i doses administered alone, and coadministration of DGAT2i + ACCi, compared to placebo, and the		Occurrence of any one of the following over time up to Week 48: • all-cause mortality

Table 6. Additional Tertiary/Exploratory Objectives and Endpoints

Objectives	Estimands	Endpoints
coadministration of DGAT2i + ACCi relative to DGAT2i alone, *over time on the incidence of hepatic outcomes*		• hepatic decompensation events (ie, hepatic encephalopathy, variceal bleeding, • development of ascites requiring treatment) • histological progression to cirrhosis • increase of MELD-Na score from ≤12 to ≥15 indicating listing for liver transplant
To evaluate the effect of a range of DGAT2i doses administered alone, and coadministration of DGAT2i + ACCi, compared to placebo, and the coadministration of DGAT2i + ACCi relative to DGAT2i alone, *overtime on the incidence of cardiovascular outcomes*		Occurrence of morbidity and mortality and CV endpoints (MACE) over time up to Week 48
To evaluate the effect of a range of DGAT2i doses administered alone, and coadministration of DGAT2i + ACCi, compared to placebo, and the coadministration of DGAT2i + ACCi relative to DGAT2i alone, on various patient reported outcomes		Change from baseline, over time, on the following endpoints • abdominal pain and bloating questions from the NASH Symptom Diary • fatigue, sleep disturbance, and daytime sleepiness questions from the NASH Symptom Diary • fatigue as measured by PROMIS Fatigue Custom 9-Item Version questionnaire • HRQoL sub-scale scores as measured by NASH-Check • NASH PGI-S In addition, summary of absolute score, by time, of • NASH PGI-S • NASH PGI-C
To enable the exploratory research through collection of CCI [redacted], unless prohibited by local regulations or ethics committee decision		CCI [redacted] to permit retrospective analysis of CCI [redacted] • These results may or may not be generated in the context of the present study

Continuous endpoints over time

A MMRM will be used for the analysis of continuous endpoints with more than one post-baseline collection time point. All observed data collected during the post-baseline treatment period will be utilized. The MMRM analysis will be performed with treatment, study week (nominal timepoint) and treatment-by-study week interaction as fixed effects, and baseline value of the analysis endpoint. If the endpoint being analyzed is log-transformed, the baseline value of the analysis endpoint will also be log-transformed. Repeated measures model with unstructured correlation matrix will be utilized. If this does not converge then compound symmetry structure will be considered. Additionally, the number of covariates may be reduced to improve model fit. Estimates of treatment effects will be assessed using LSMs and CIs at each time point. LSM difference for each comparison along with the corresponding 95% CI will be provided. If there are major deviations from the statistical

assumptions underlying this model then alternative transformations (eg, log) or non-parametric analyses may be presented.

Event-based endpoints

The occurrence of hepatic events, and morbidity and mortality and CV endpoints (MACE) over time up to Week 48 will be summarized descriptively by treatment group.

9.5. Interim Analyses

Interim analyses will be performed ***to assess safety,*** at a minimum, after approximately 33%, 67%, and 100% of planned total sample size (in Protocol Amendment 1), has been randomized in the study. As such, the 1st trigger for safety review remains at approximately the same number randomized as Original Protocol (approximately 25% randomized ie, 112/450 vs 115/350 = 33% in Protocol Amendment 1). Interim analysis results may be used for internal business decisions regarding future study planning, conducting a sample size re-estimation, or adapting the safety-related endpoints in the study after the interim analysis, or early unblinding to facilitate Population PK/PD model development. Before any interim analysis is instigated, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind as per Pfizer's SOPs will be documented and approved in an E-DMC charter. In addition, the analysis details will be documented and approved in an interim analysis SAP or final SAP.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an E-DMC, Adjudication Committee, and a steering committee.

- The **E-DMC** is independent of the study team and includes only external members (consisting of at least 1 cardiologist, 1 endocrinologist, 1 gastroenterologist or hepatologist, and 1 statistician). The E-DMC charter describes the role of the E-DMC in more detail.
    - The E-DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.
- An independent **Adjudication Committee** consisting of external experts performing *blinded* review of ***all*** potential events highlighted below and *further specified* in the Adjudication Committee Charter, to confirm that the data support the endpoint designation –
    - Fatal events: Liver-related death, cardiovascular death, or other death;
    - Hepatic events: including but not limited to hepatic decompensation events [ie, hepatic encephalopathy, hospitalization for variceal bleeding, development of

ascites requiring treatment], histological progression to cirrhosis, increase of MELD-Na score from ≤12 to ≥15 indicating listing for liver transplant, HCC, drug-induced liver injury;

- Cardiovascular events: including but not limited to major adverse cardiovascular events – ie, nonfatal myocardial infarction, nonfatal stroke, cardiovascular death; plus, hospitalization for unstable angina – ie, heart failure, transient ischemic attack, revascularization.

- A blinded **Steering Committee** comprising of both external and internal (ie, Pfizer) medical/clinical representatives from each country/region of study operations who will oversee recruitment, retention, and quality issues within the country/region.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

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 authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant. Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

A separate signature will be required to document a participant's agreement to allow specimens to be used for additional research. Participants who decline to participate in this optional additional research will not provide this separate signature.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is

responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic form and are password protected to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (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 provided in the study monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly

provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. 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 site.

Data reported on the CRF or entered in the eCRF that are 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 clinical monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.8. 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 date of the first participant's first visit 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 upon notification to the sponsor if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC 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 ECs/IRBs, the regulatory authorities, and any CRO(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.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results from this study are envisioned to be presented, separately, at scientific meetings – as determined *jointly* by the sponsor and member(s) of the Steering Committee. Beyond this, the results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement. Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it

should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

Table 7. Protocol-Required Safety-Related Laboratory Assessments and Exploratory Biomarkers in Study C2541013

Hematology	Chemistry	Urinalysis	Other
–Hemoglobin –Hematocrit –RBC count –Reticulocyte count (Abs) –MCV –MCH –MCHC –Platelet count –WBC count –Total neutrophils (Abs) –Eosinophils (Abs) –Monocytes (Abs) –Basophils (Abs) –Lymphocytes (Abs)	–BUN –Creatinine –*Plasma* glucose –Calcium –Sodium –Potassium –Chloride –Total CO_2 (Bicarbonate) –AST (SGOT) –ALT (SGPT) –Alkaline phosphatase –GGT –Total Bilirubin –Direct (conjugated) bilirubin –Indirect (unconjugated) bilirubin –Total bile acids –Creatine Kinase –Uric acid –Albumin –Total protein	–pH –Glucose (qual) –Protein (qual) –Blood (qual) –Ketones –Nitrites –Leukocyte esterase –Urobilinogen –Urine bilirubin –Microscopy[a]	–Cystatin-C (and eGFR using CKD-EPI-Cystatin-C) –Plasma aPTT, PT, INR –Serum FSH[b] –Serum and urine pregnancy test (Section 8.2.6) –Urine drug test[c] –α1-antitrypsin[d] –Ceruloplasmin[d] –Serology[d]: HBsAg, HCVAb (and if positive, reflex HCV RNA), HIV –%CDT[e] –HbA1C –Fasting serum Lipid Panel[f] –Adiponectin
Additional exploratory biomarker assessments[g] include: –Serum apolipoproteins A1, B(total), B100, B48, C3, E and *direct* VLDL –Plasma Insulin –hs-CRP –CK18-M30, CK18-M65 –ProC3 and ProC6 –Plasma PCSK9 –ELF Test CCI [redacted] **Additional Tests** – needed for instances of suspected Hy's law –refer to Appendix 6			

a. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase
b. In females, at PreQ, and SCR1, *only*
c. At PreQ, SCR1, and Visit 4/Baseline, *only*; minimum requirement for urine drug test include cocaine, opiates/opioids, benzodiazepines and amphetamines; this test *not* permitted to be repeated at scheduled visits.
d. At PreQ, and SCR1, *only*
e. At PreQ, SCR1, Visit 4/Baseline, Day 1/Visit 5, Week 48/Visit 19, and when study intervention is prematurely stopped (with participant remaining in study *or* permanently withdrawn)
f. Includes triglycerides, HDL-C, *direct* LDL-C, and total cholesterol
g. At selected visits starting from Visit 4/Baseline though 1st on-site Follow-up/Visit 20, inclusive, per SoA-Table A2

For list of terms corresponding to the abbreviations used herein, refer to Appendix 13

Table 7 delineates the protocol-mandated safety-related laboratory tests and exploratory biomarkers. The required blood and urine collections will be performed at times defined in the SoA-Table A2.

Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the sponsor-identified central laboratory(ies), or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will ***not*** be reported to investigator sites or other blinded personnel until the study has been unblinded.

CCI : Due to current restrictions to ship human genetic samples outside of CCI, and as the sponsor's diligence did not identify a comparable assay in CCI to the one planned for use in the study, the following will apply to all participants consented in CCI –

- samples for analyzing ProC3 and ProC6 will *not* be collected;
- assessment of direct VLDL will be ***removed*** from the fasting lipid panel analysis;
- summarization of these parameters will *not* include any data from participants consented and randomized in CCI

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

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
  - Is associated with accompanying symptoms.
  - Requires additional diagnostic testing or medical/surgical intervention.
  - Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are Aes. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

An SAE is defined as any untoward medical occurrence that, at any dose:
Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. • Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the CT SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	• All AEs/SAEs associated with exposure during pregnancy or breastfeeding • Occupational exposure is not recorded.	*Note*: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the

AE and SAE Recording/Reporting

exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- ***Mild:*** An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- ***Moderate:*** An event that causes sufficient discomfort and interferes with normal everyday activities.
- ***Severe:*** An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both Aes and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.

Assessment of Causality

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

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

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

No contraception methods are required for male participants in this study, CCI [redacted]

For CCI ***only:*** although no contraception methods are required for male participants in the other countries/regions, based on a specific requirement from the regulatory authority in CCI, male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention:

- Refrain from donating sperm
- PLUS ***either*** –
  - Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.

  OR
  - Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.
- Other sections of the protocol relevant to the requirement for contraception in male participants include Section 4.2.1 and Section 5.4.1 and considered to be updated in accordance with text highlighted above.
- An EDP also occurs if a male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception – refer to Section 8.3.5.

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), ***preferably*** with low user dependency, as described below during the intervention period and for ***at least 28 days*** after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

    For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

    NOTE: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
        - High FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
        - Female on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

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

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner:

   - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

   - Oral;

   - Intravaginal;

   - Transdermal.

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

   - Oral;

   - Injectable.

8. Sexual abstinence:

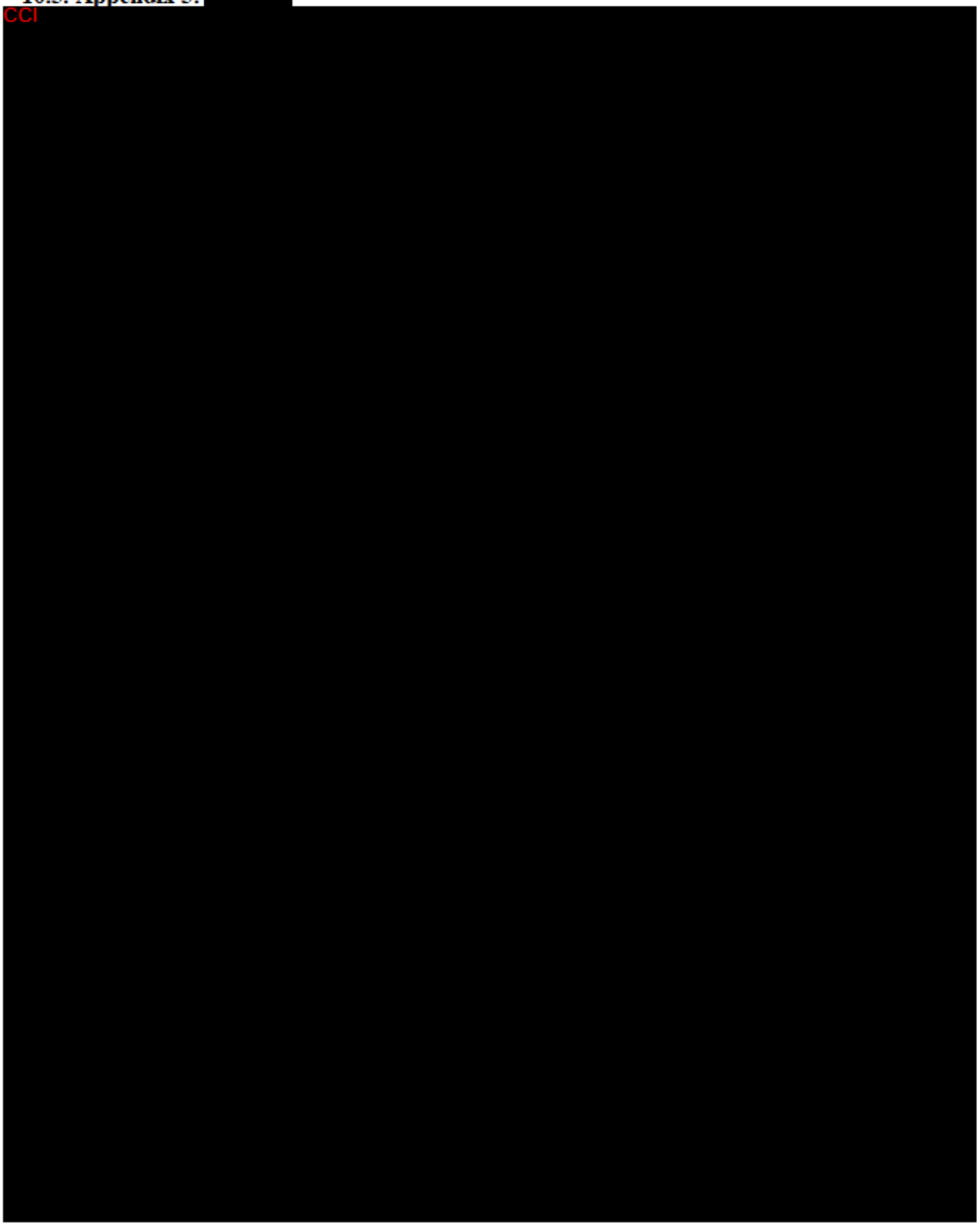
   - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

In addition, *one* of the following effective barrier methods must also be used when option 6 or 7 are chosen above:

- Male *or* female condom with or without spermicide;
- Cervical cap, diaphragm, *or* sponge with spermicide;
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

10.5. Appendix 5: CCI

CCI



10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as Adverse Events
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 msec. • New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration. • Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That May Qualify as Serious Adverse Events

• QTcF prolongation >500 msec.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS >120 msec).
• New-onset right bundle branch block (QRS >120 msec).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptom-free patients with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm (such as torsades de pointes)).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as Serious Adverse Events

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all-inclusive of what to be reported as AEs/SAEs.

10.8. Appendix [redacted] Inhibitors and Inducers

This list is not considered as exhaustive. Any questions regarding use of [redacted] inhibitors and inducers should be directed to the sponsor study team.

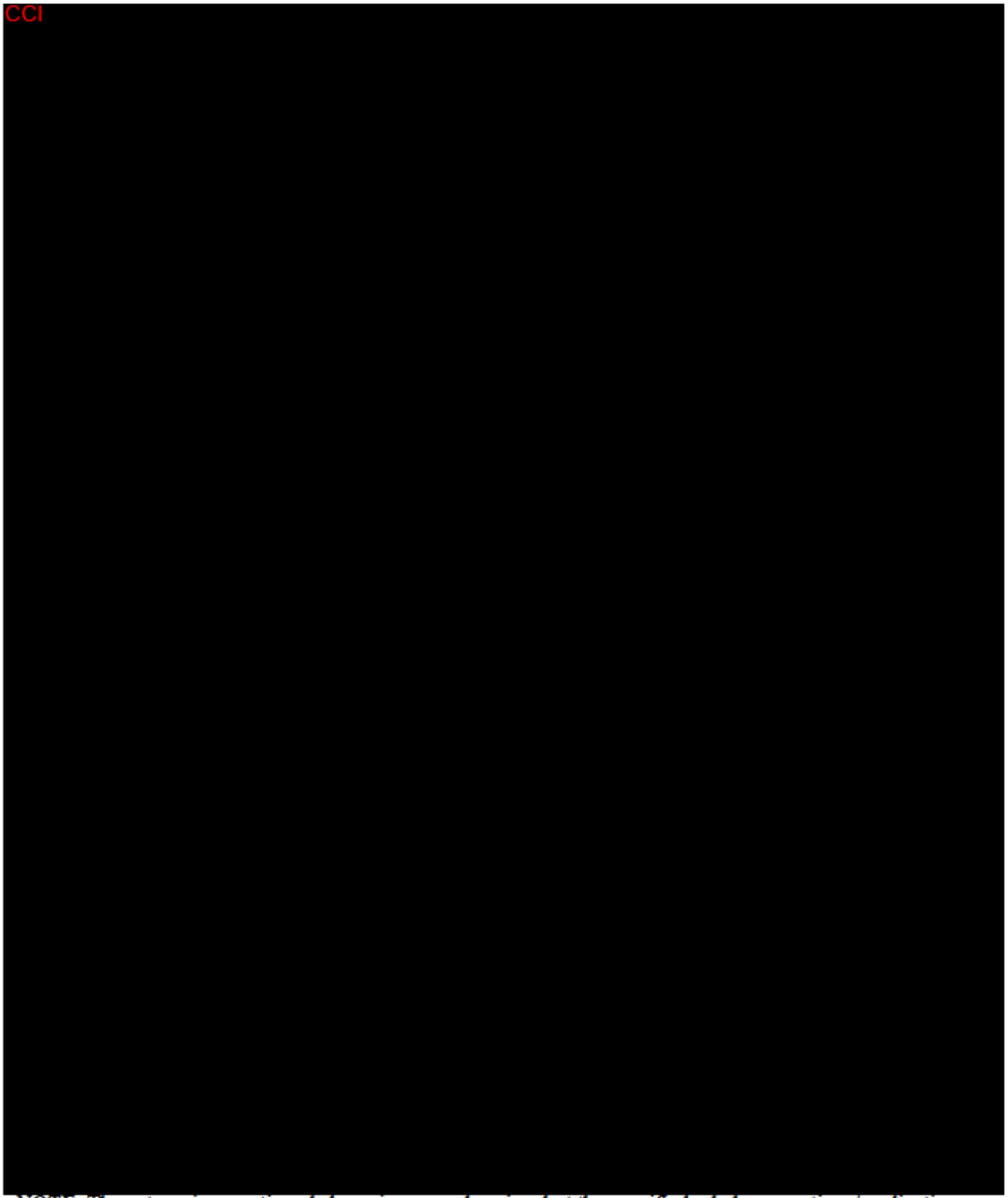
[redacted] Inhibitors	[redacted] Inducers
HIV antivirals	**HIV antivirals**
Indinavir	Nevirapine
Nelfinavir	**Miscellaneous**
Ritonavir	Barbiturates
Saquinavir	Carbamazepine
Boceprevir	Glucocorticoids (systemic)
Lopinavir/ritonavir	Oxcarbazepine
Amprenavir	Phenobarbital
Atazanavir	Phenytoin
Telaprevir	Rifabutin
Darunavir/ritonavir	Rifampin
Fosamprenavir	St. John's wort[3]
Tiprinavir/ritonavir	Troglitazone
Antibiotics	Nafcillin
Clarithromycin	Avasimibe[4]
Troleandomycin	Enzalutamide
Telithromycin	Mitotane
Anti-infective	
Itraconazole	
Ketoconazole	
Posaconazole	
Voriconazole	
Miscellaneous	
Nefazodone	
Grapefruit juice[1]	
Conivaptan	
Mibefradil[2]	
Idelalisib	

1. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "[redacted] inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).
2. Withdrawn from the United States market.
3. The effect of St. John's wort varies widely and is preparation-dependent.
4. Not a marketed drug.

Reference: U.S. Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers, available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

For [redacted] only: In response to the uniquely disproportionate use of herbal preparations, along with unique concomitant medications only available in [redacted], in the population being enrolled in this study, the following clarifications regarding the use of herbal preparations and [redacted]-specific concomitant medications, is offered; these changes are guided by a

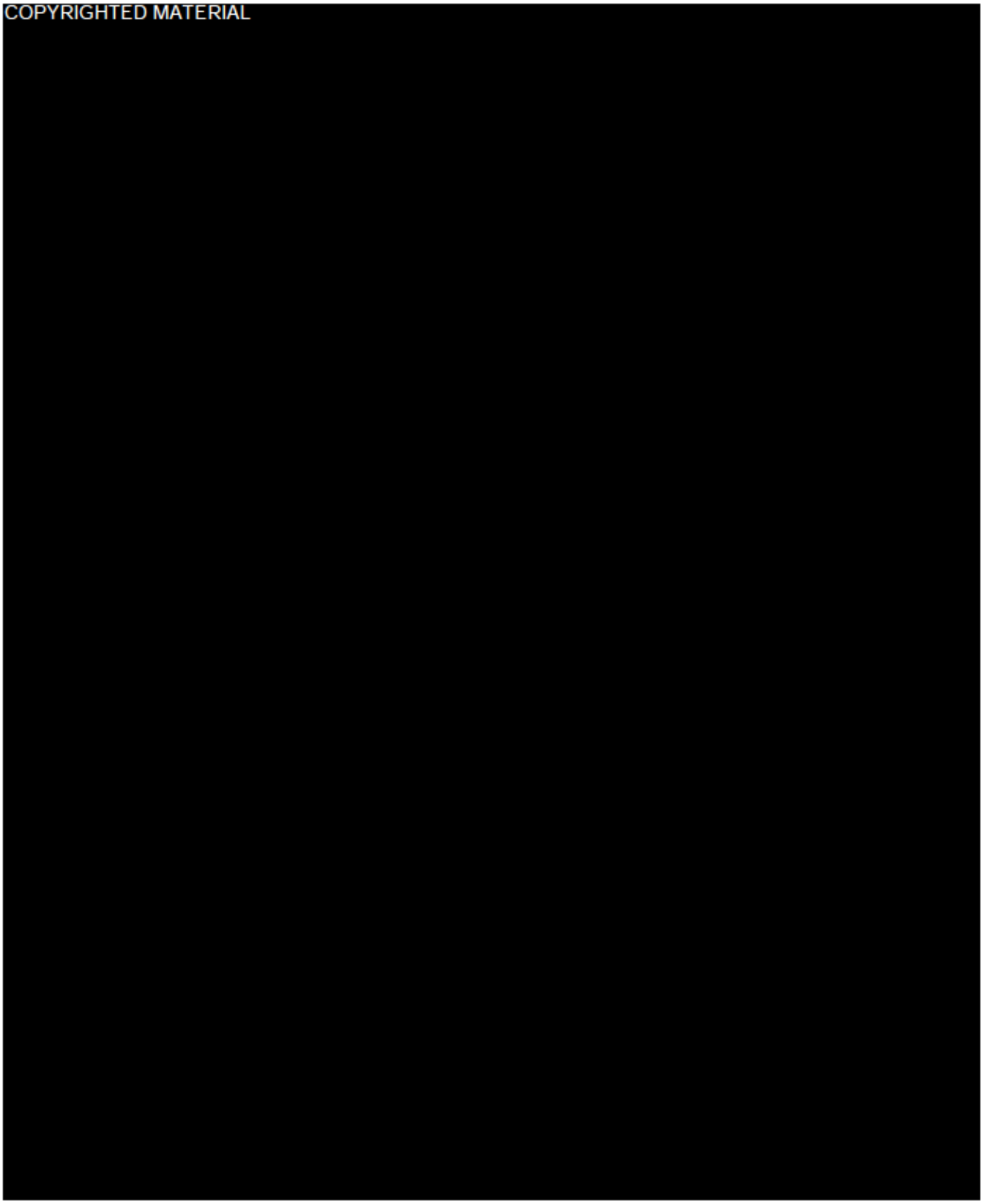
comprehensive review of the available/accessible literature regarding each of the herbal components -

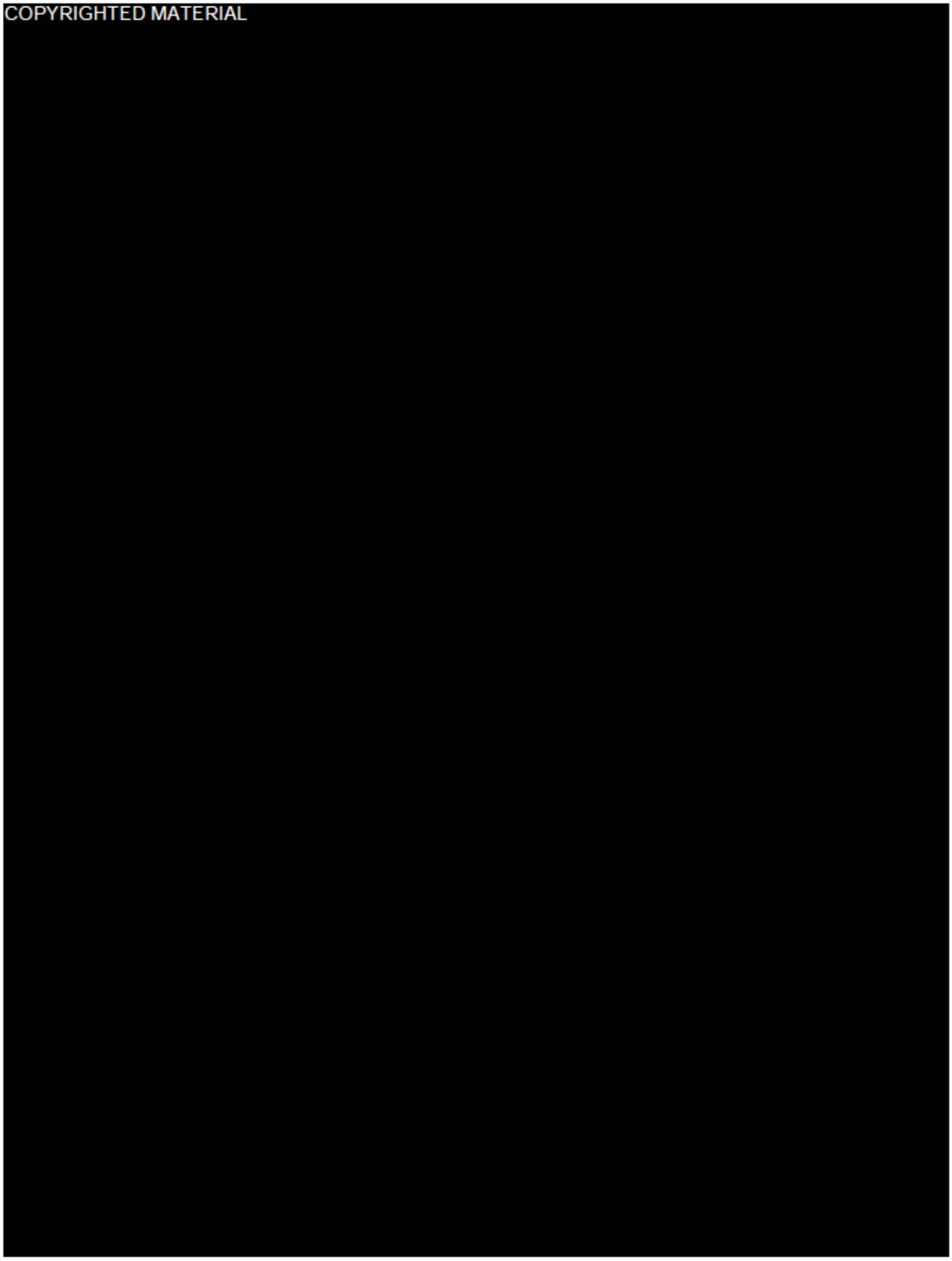


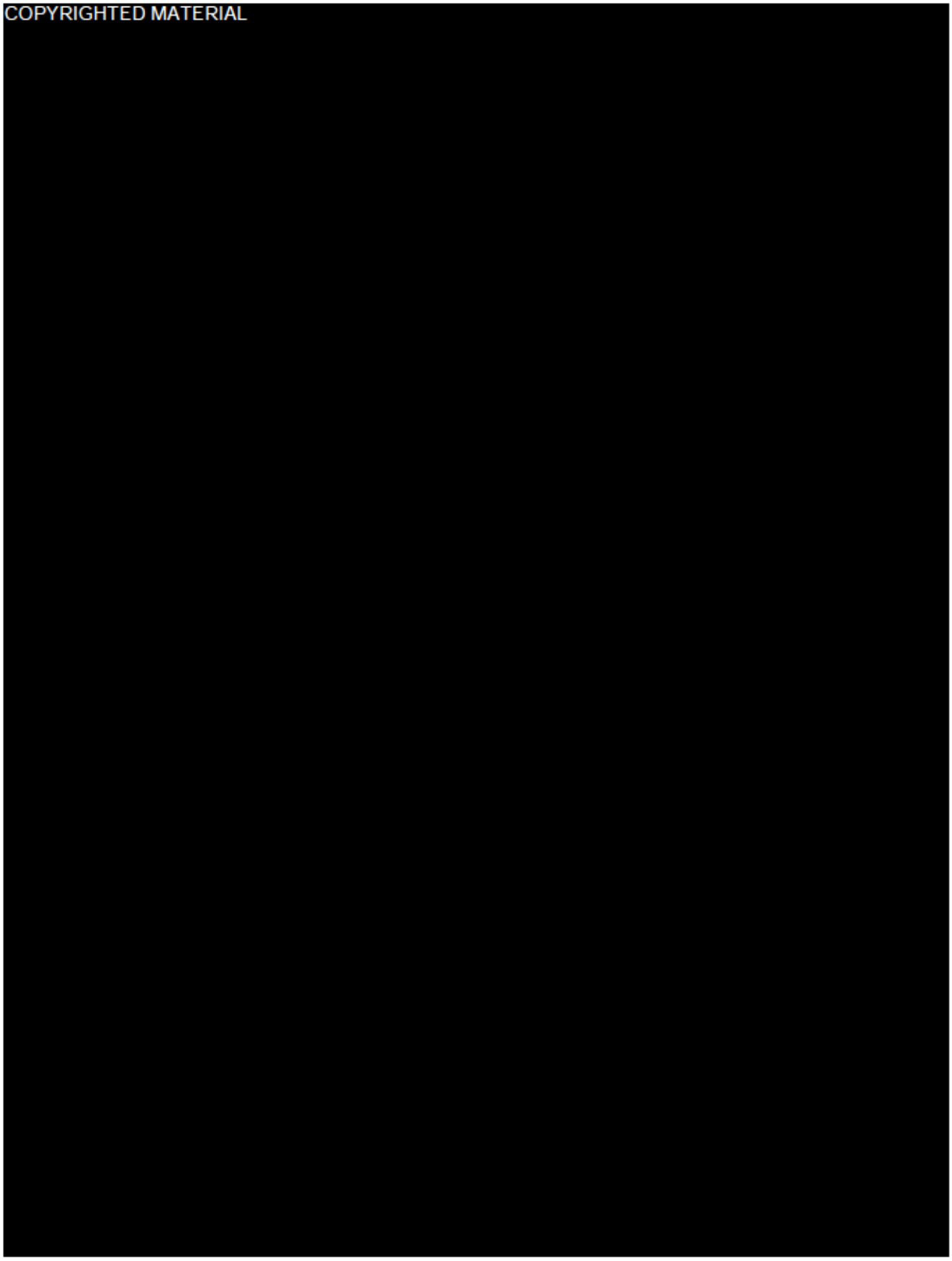
NOTE: The categories mentioned above is comprehensive, but the specific herbal preparations/medications is not all inclusive and example of agents offered are illustrative – these may or may not be available in CCI The Sponsor should be consulted in determining whether or not it is permitted to use specific herbal preparation/concomitant medication not included herein.

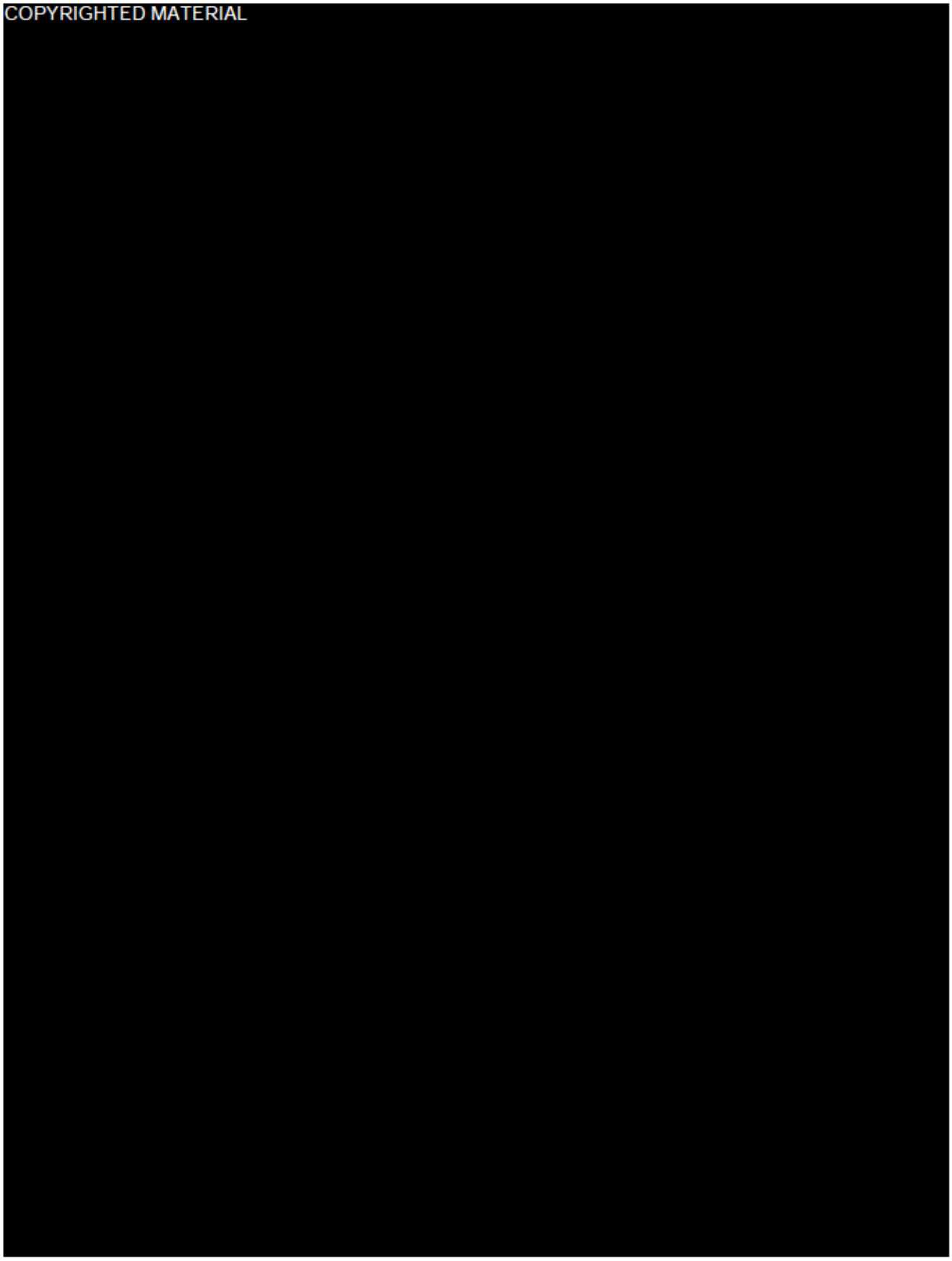
10.9. Appendix 9: Patient-Reported Outcomes

10.9.1. NASH CHECK

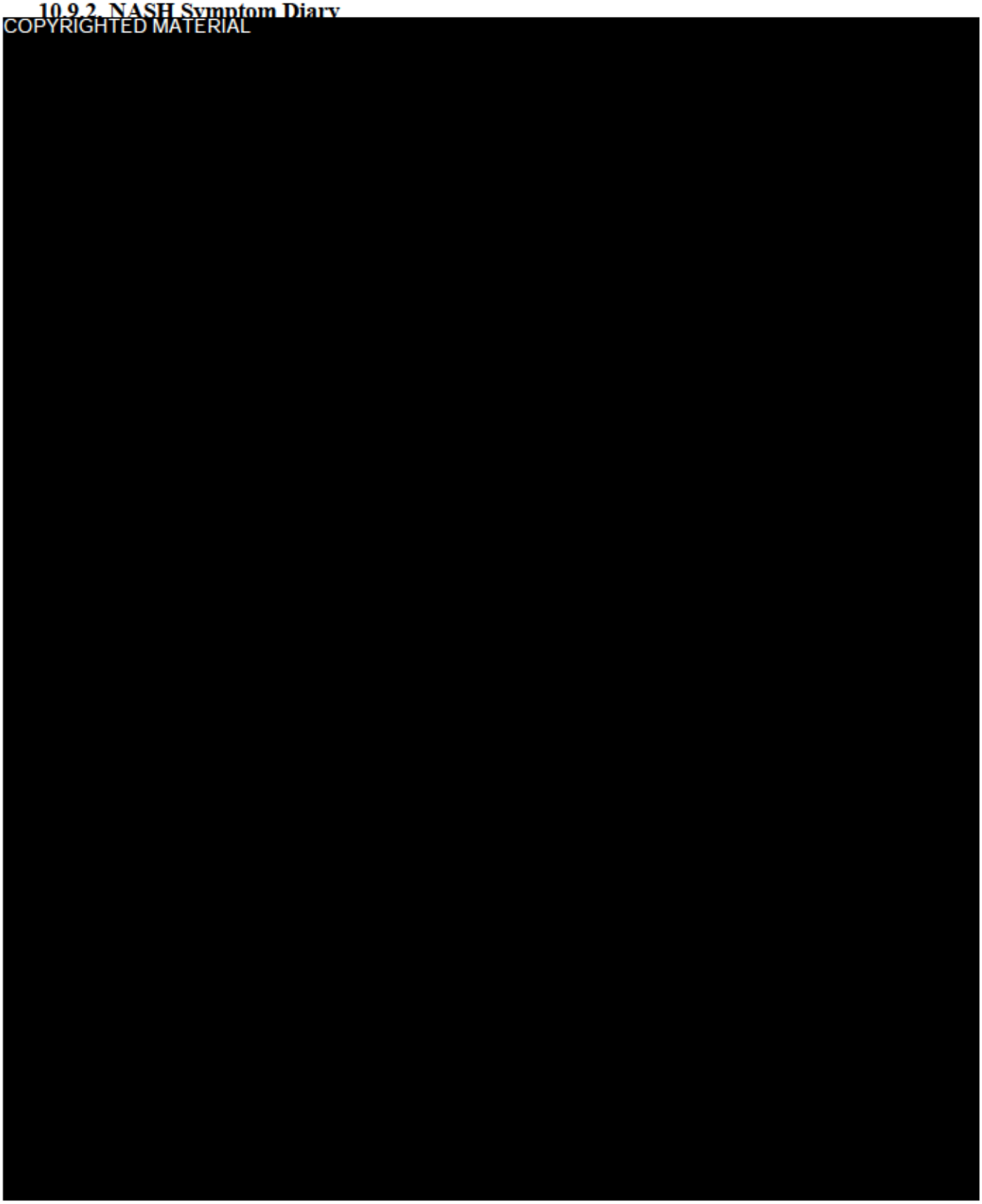


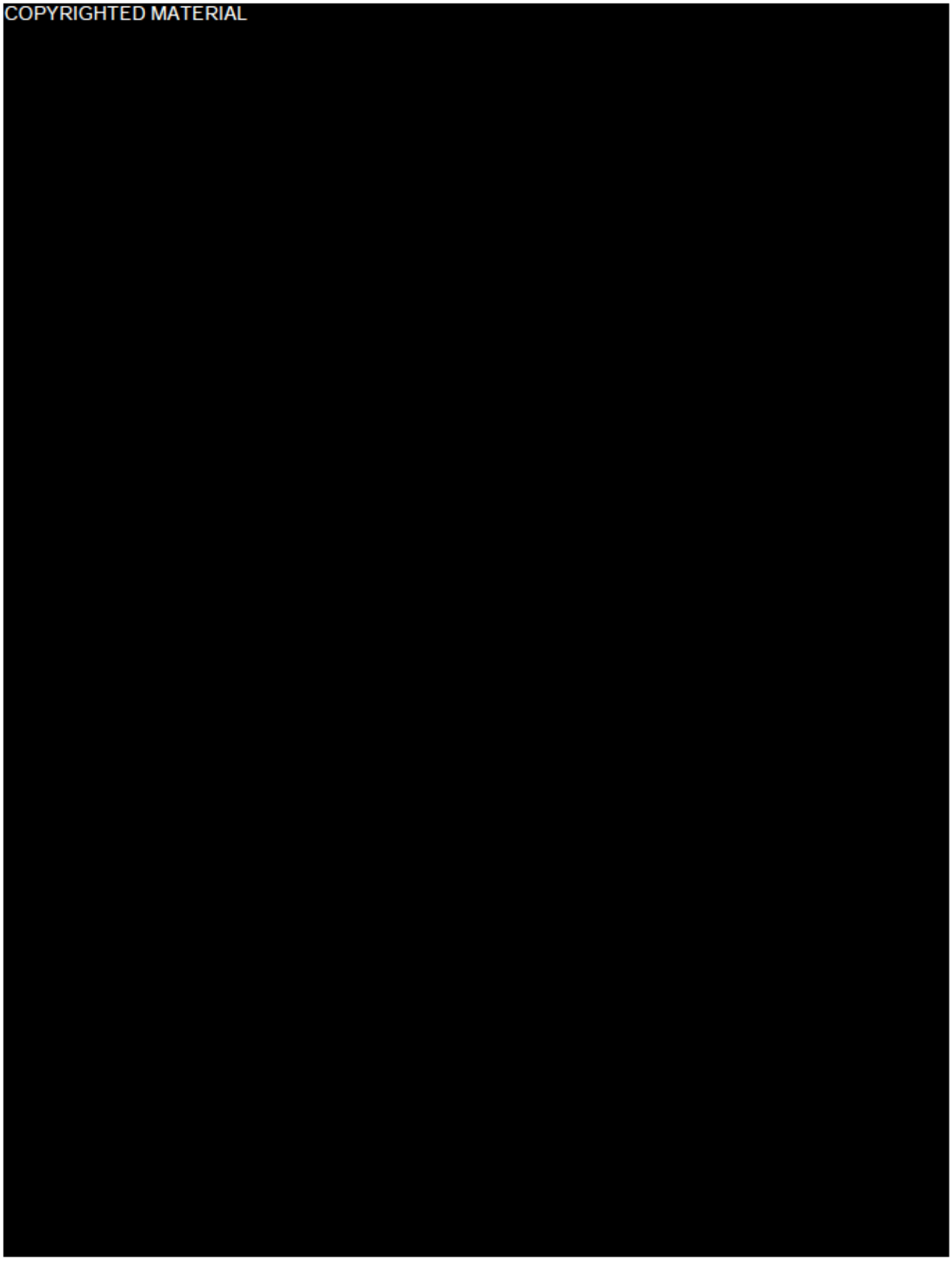






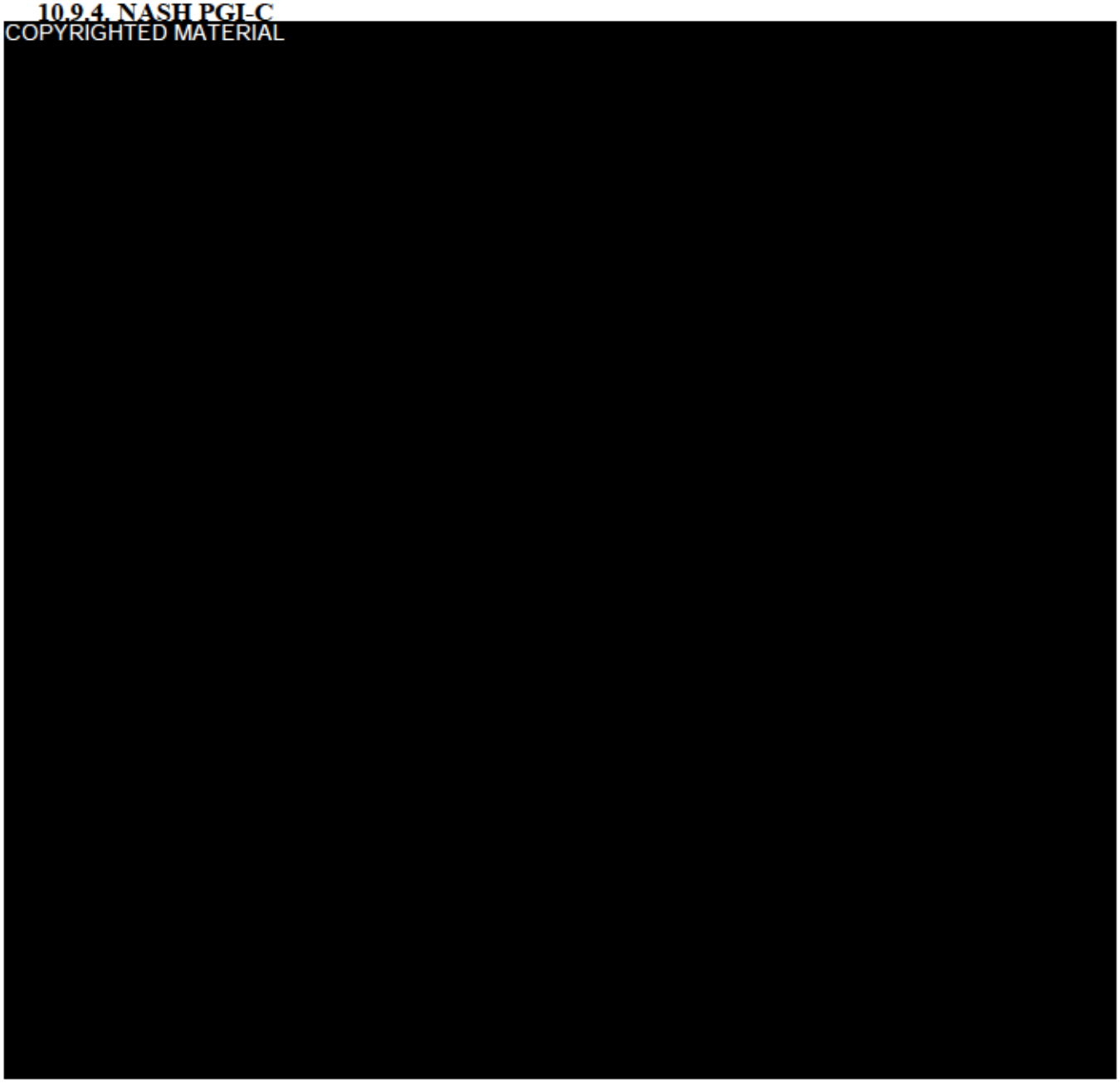
10.9.2. NASH Symptom Diary





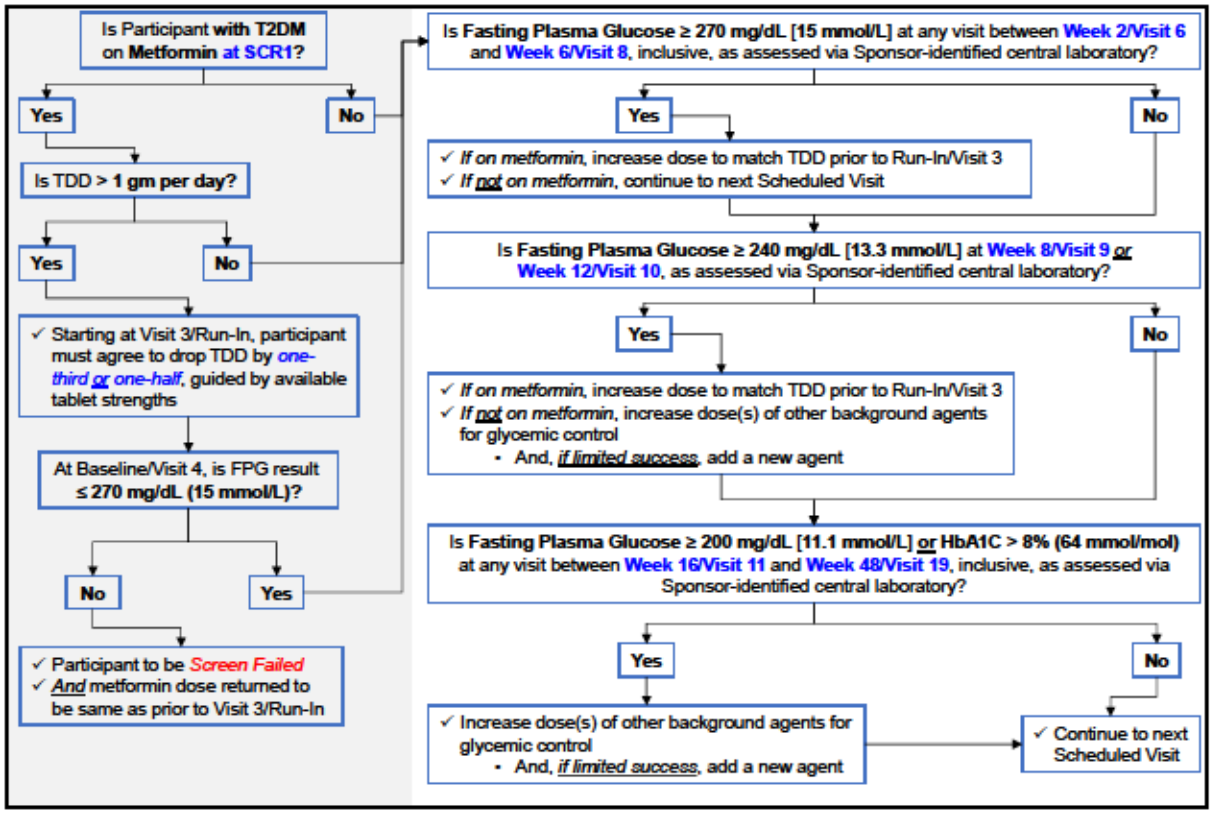
10.9.3. NASH PGI-S

10.9.4. NASH PGI-C



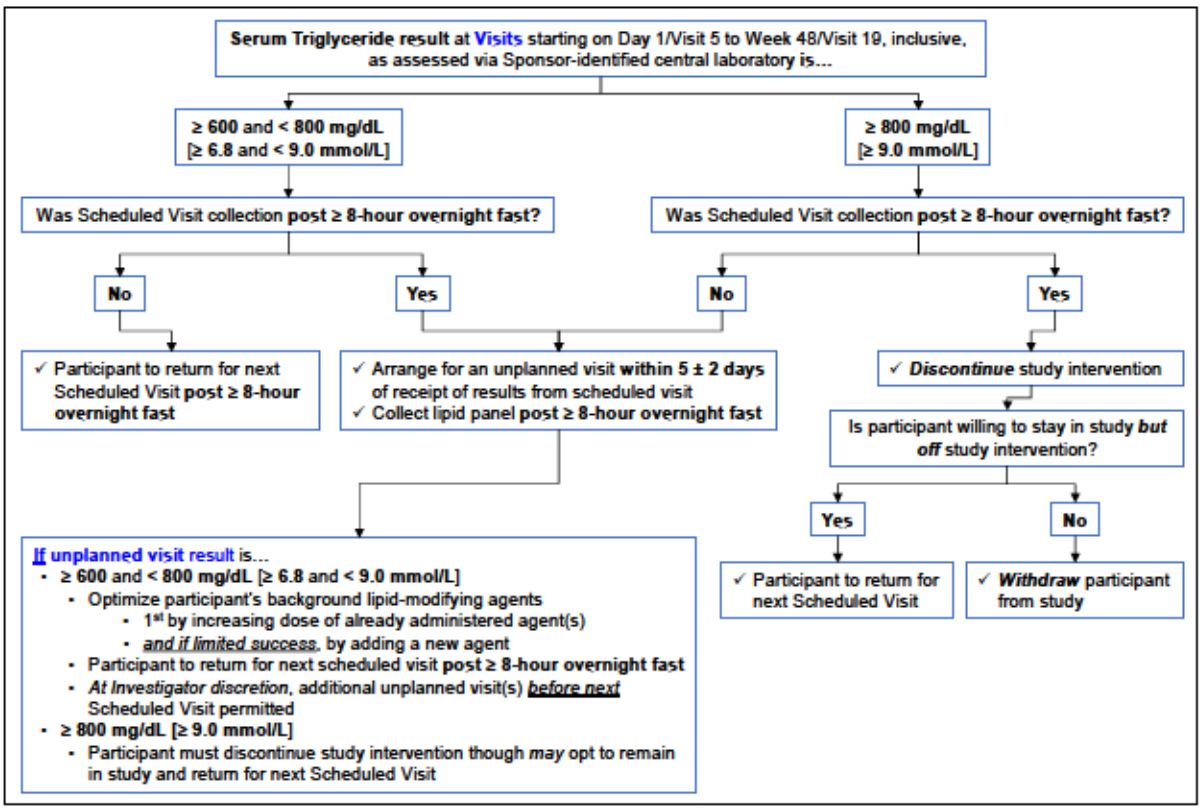
10.9.5. PROMIS FATIGUE Custom 9-Item Version

10.10. Appendix 10: Guidance to Investigators – Management of Individual Participants Glycemic Control – *including Metformin Dose Starting at Run-In/Visit 3*

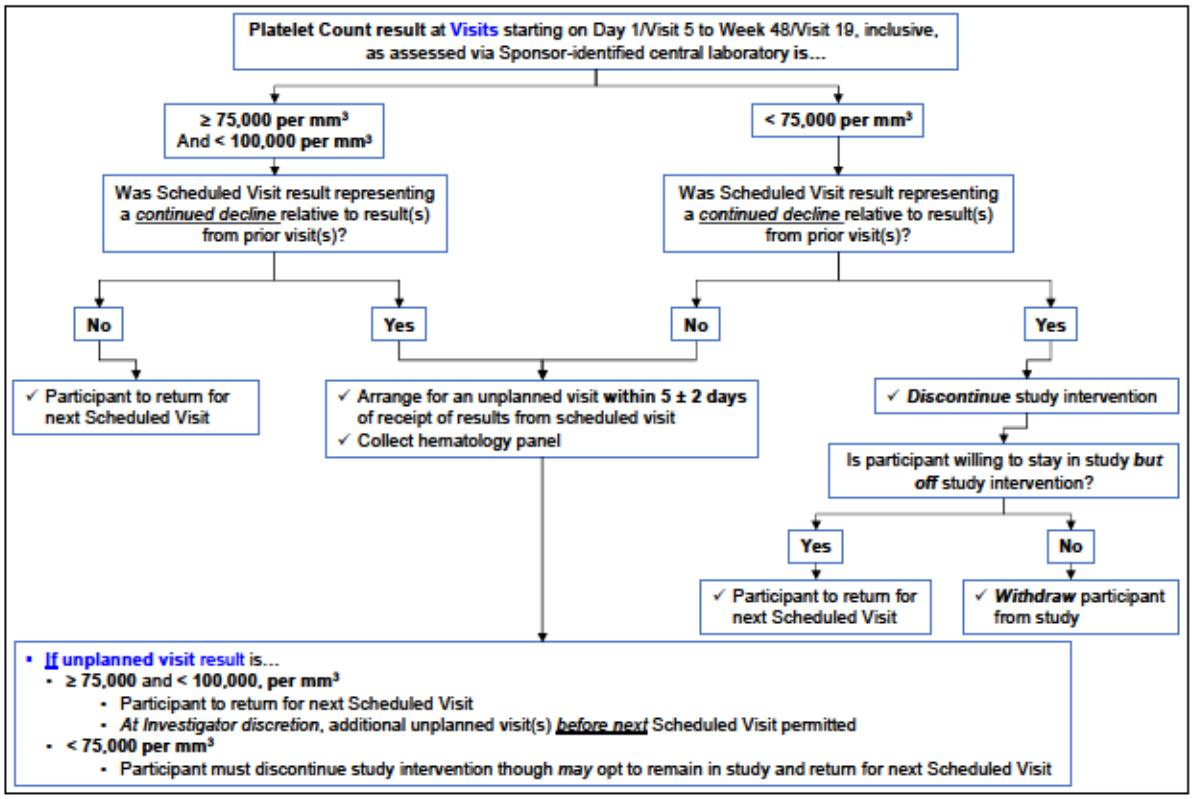


In participants in whom metformin dose is adjusted at Run-In/Visit 3, blood collections at Week 2/Visit 6, Week 6/Visit 8, and Week 12/Visit 10 can include assessment of FPG ± HbA1C (beyond at the timepoints listed in SoA-Table A2), to aide evaluation per guidance above.

10.11. Appendix 11: Guidance to Investigators – Management of Individual Participants With Elevation in Fasting Serum Triglycerides



10.12. Appendix 12: Guidance to Investigators – Management of Individual Participants With Decrease in Platelet Count



10.13. Appendix 13: Abbreviations

The following abbreviations may be used in the protocol –

Abbreviation	Term
%CDT	percent carbohydrate deficient transferrin relative to total transferrin
A1AT	Alpha-1-antitrypsin
CCI	[redacted]
Abs	absolute
ACC	acetyl-CoA carboxylase
ACCi	acetyl-CoA carboxylase inhibitor (PF-05221304)
AE	adverse event
CCI	[redacted]
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	Analysis of Covariance
Apo	apolipoprotein
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC_{0-24}	area under the concentration-time curve from time 0 to 24 hours
AUC_{24}	area under the concentration-time curve from time 0 to 24 hours
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
AUC_{tau}	area under the concentration-time curve from time 0 to end of dosing period
AUDIT	Alcohol use disorders identification test
AV	atrioventricular
CCI	[redacted]
BCRP	breast cancer resistant protein
BID	bis in die (twice-a-day)
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CAP™	Controlled attenuation parameter
C_{avg}	Average plasma concentration
CDT	Carbohydrate deficient transferrin
CFR	code of federal regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine Kinase
CK18-M30	cytokeratin-18-M30 fragment
CK18-M65	cytokeratin-18-M65 fragment
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation
C_{max}	peak or maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
CoA	coenzyme A
conmeds	concomitant mediations
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease of 2019
CRF	Case Report Form
CRN	Clinical Research Network
CRO	contract research organization
CSR	clinical study report

Abbreviation	Term
CT	clinical trial
C_{trough}	plasma concentration before next dose
CV	cardiovascular
CYP	Cytochrome P-450 (3A, 2B6, 2C9, 2C19)
D/C	discontinue
DAG	diacylglycerol
dB/m	decibels per meter
DCCT	Diabetes Control and Complications Trial
DGAT1	diacylglycerol acyltransferase 1
DGAT2	diacylglycerol acyltransferase 2
DGAT2i	diacylglycerol acyltransferase 2 inhibitor (PF-06865571)
DILI	drug-induced liver injury
CCI	
DNL	de novo lipogenesis
DPPIV	Dipeptidyl peptidase-IV
DU	Dispensing Unit
E_0	placebo responder rate
EC	ethics committee
EC_{50}	concentration of the drug at half maximum response
ECG	electrocardiogram
eCRF	Electronic case report form
ED_{50}	Dose that produces half maximum drug effect
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EFD	embryo-fetal developmental
eGFR	Estimated glomerular filtration rate
ELF	Enhanced Liver Fibrosis
EMA	European Medical Agency
E_{max}	maximum effect of drug
ePRO	Electronic Patient Reported Outcome
EU	European Union
EUA	Emergency Use Authorization
EudraCT	European Clinical Trials Database
F/U	Follow-up
F2	Significant stage of fibrosis when scarring has occurred and extends outside the liver area
F3	Severe stage of fibrosis with spreading and forming bridges with other fibrotic liver areas
FAST™	Derived score (using CAP™, VCTE™, and AST) to identify those with progressive NASH
FDA	Food and Drug Administration
FFA	Free fatty acid
FPG	Fasting plasma glucose
FPI	Fasting plasma insulin
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
GLP1r	glucagon-like peptide 1 receptor
HbA1C	Glycated hemoglobin
HBsAg	hepatitis B surface antigen
HCC	Hepatocellular carcinoma
HCV RNA	Hepatitis C virus genetic material (ie, Ribonucleic acid)
HCVAb	hepatitis C virus antibody
HDL	High density lipoprotein

Abbreviation	Term
HDL-C	high density lipoprotein cholesterol
HIPPA	The Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HOMA-IR	Homeostatic model assessment of insulin resistance
HR	Heart rate
HRQoL	health-related quality of life
HRT	hormone replacement therapy
hs-CRP	High-sensitive C-reactive protein
CCI	[redacted]
IB	Investigator's brochure
IC_{50}	Concentration that results in 50% of inhibitory effect
ICD	informed consent document
ICH	International Conference on Harmonisation
ID	identification
IL	Interleukin
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IPAL	Integrated Path to Architectural Licensure
IRB	institutional review board
IRT	interactive response technology
IWR	interactive web response
JAK	Janus Kinase
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
kPa	kilopascals
LDL-C	low density lipoprotein-cholesterol
LFT	liver function test
LLN	lower limit of normal
LS	least square
LSM	Least Square Means
MACE	major adverse cardiovascular event
MATE	multidrug and toxin extrusion protein
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	medical Dictionary for Regulatory Activities
MELD-Na	model of end-stage liver disease including serum sodium (in addition to serum creatinine, bilirubin, and INR)
MIRNA	Metabolic Interventions to Resolve NASH with Fibrosis
MMRM	Mixed model repeated measure
MR	magnetic resonance
MRI	magnetic resonance imaging
MRI-PDFF	Magnetic resonance imaging using proton density fat fraction acquisition
msec	millisecond
MTD	maximum tolerated dose
N/A	not applicable
NAFLD	nonalcoholic fatty liver disease
NAS	NAFLD Activity Score
NASH	Nonalcoholic steatohepatitis
NGSP	National Glycohemoglobin Standardization Program
NOAEL	no observed adverse effect level
non-HDL	non-high density lipoprotein cholesterol

Abbreviation	Term
NRS	numeric rating scale
NSAIDs	Non-steroidal anti-inflammatory drugs
CCI	
NYHA	New York Heart Association
CCI	
PACL	Protocol Administrative Clarification Letter
PCSK9	proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamic
PE	physical exam
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
P-gp	P-glycoprotein
CCI	
PI	principal investigator
PK	pharmacokinetics
PK/PD	pharmacokinetic-pharmacodynamic
PNPLA3	Patatin like phospholipase domain containing protein 3
PPARγ	Peroxisome proliferator-activated receptor gamma
PreQ	Prequalification visit
PRO	Patient Reported Outcome
ProC3	N-terminal propeptide of type III procollagen
ProC6	C-terminal fragment of α3 chain of procollagen type VI
PROMIS	Patient-Reported Measurement Outcome Information System
PT	prothrombin time
PVC	premature ventricular contraction
Q12H	Every 12 hours (eg, dosing)
Q8H	every 8 hours
QD	quaque die (once-a-day)
QRS	Combination of Q-, R- and S- wave on an electrocardiogram representing ventricular depolarization
QSP	Quantitative systems pharmacology
QTc	QT interval corrected for heart rate
QTcF	Fridericia's formula, a correction formula for the QC interval
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-COV-2	Severe acute respiratory syndrome coronavirus 2
SCR1	Screen 1 / Visit 1
SCR2	Screen 2 / Visit 2
SD	Standard deviation
SGLT2	Sodium-glucose cotransporter 2
SGOT	serum glutamic oxalo-acetic transaminase
SGPT	serum glutamic pyruvic transaminase
CCI	
SoA	Schedule of Activities
SOP	standard operating procedure
SRSD	single reference safety document

Abbreviation	Term
SSID	Single subject identifier
SUSAR	suspected unexpected serious adverse reaction
SVR	Sustained virology response
T	Telephone contact
$t_{1/2}$	terminal half-life
CCI	[redacted]
T2DM	type 2 diabetes mellitus
TBili	total bilirubin
TDD	Total daily dose
TEAE	Treatment-emergent adverse event
TG	triglyceride
TI	therapeutic index
TNF	Tumor Necrosis Factor
Tyr285X	Tyrosine 285 mutation
ULN	upper limit of normal
US	United States
VCTE™	Vibration-Controlled Transient Elastography
VLDL	very low-density lipoprotein
VRS	Verbal rating scale
WBC	white blood cell
WOCBP	Women of childbearing potential

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