A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Pharmacodynamic Effects of MEDI0382 in Obese Subjects With Non-alcoholic Fatty Liver Disease (NAFLD)/ Non-alcoholic Steatohepatitis (NASH)

Sponsor Protocol Number: D5671C00002

Application Number: IND number: 139975

Investigational Product: MEDI0382 (cotadutide)

Sponsor: MedImmune Limited, a wholly owned subsidiary of AstraZeneca, PPD Cambridge, CB21 6GH, UK

Medical Monitor: PPD
Medical Monitor, AstraZeneca
Phone: PPD

Protocol History, Date:
Original Protocol, 15March2019
Protocol Amendment 1, 17May2019
Protocol Amendment 2, 19Jul2019
Protocol Amendment 3, 19Aug2019
Protocol Amendment 4, 26Feb2020
Protocol Amendment 5, 20Apr2020
Protocol Amendment 6, 27Nov2020

PROTOCOL SYNOPSIS

TITLE

A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Pharmacodynamic Effects of MEDI0382 in Obese Subjects With Non-alcoholic Fatty Liver Disease (NAFLD)/Non-alcoholic Steatohepatitis (NASH)

HYPOTHESES

Primary Hypothesis:

MEDI0382 will have an acceptable safety (including hepatic safety) and tolerability profile in subjects with NAFLD/NASH

Secondary Hypothesis:

Treatment with any one dose of MEDI0382 tested will lead to a reduction in hepatic fat in subjects with NAFLD/NASH

OBJECTIVES AND ENDPOINTS

Type	Primary Objective	Primary Endpoint
Safety	To assess the safety (including hepatic safety) and tolerability of MEDI0382 compared with placebo	• Incidences of treatment emergent adverse events and serious adverse events through the end of the follow-up period.
Type	**Secondary Objectives**	**Secondary Endpoints**
Pharmacodynamic effects	To assess the effect of MEDI0382 on relative and absolute change in hepatic fat as assessed by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) compared with placebo	• Percent change from baseline in hepatic fat fraction (HFF) at Week 19 • Absolute change from baseline to Week 19 in HFF
[redacted]	[redacted]	CCI [redacted]
Pharmacodynamic effects	To assess the effect of MEDI0382 on circulating markers of hepatic inflammation compared with placebo	Change and percent change from baseline to Week 19 in: • alanine aminotransferase (ALT) • aspartate aminotransferase (AST) • gamma glutamyl transferase (GGT)
Pharmacodynamic effects	To assess the effect of MEDI0382 on body weight and body mass index (BMI) compared with placebo	• Change and percent change from baseline to Week 19 in body weight and BMI.

Dose response	To assess the dose response of MEDI0382 on pharmacodynamic parameters	• HFF, body weight, safety, other imaging parameters, parameters of hepatic inflammation
Immunogenicity	To evaluate the immunogenicity of MEDI0382	• Development of anti-drug antibodies (ADA) and titer (if subjects are ADA positive) during treatment and follow-up
Type	**Exploratory Objectives**	**Exploratory Endpoints**

CCI

STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, study to evaluate the safety (including hepatic safety), tolerability and pharmacodynamic effects of two dose levels of MEDI0382 in obese subjects with NAFLD/NASH. The subjects will have biopsy-confirmed NAFLD/NASH with liver fibrosis stage F1, F2 or F3. Approximately 72 subjects will be randomized across multiple study sites.

Subjects will be recruited in parallel and randomized using a 2:1:2:1 ratio:

- **MEDI0382 300 µg** – once daily subcutaneous (SC) doses of MEDI0382 300 µg (n = 24)
- **Placebo for MEDI0382 300 µg** – matched placebo (n = 12).
- **MEDI0382 600 µg** – once daily SC doses of MEDI0382 600 µg (n = 24)
- **Placebo for MEDI0382 600 µg** – matched placebo (n = 12)

Subjects will be in the study for approximately 27 weeks (189 days), including a screening period of up to 4 weeks, a 19-week treatment period, and a 4-week safety follow-up period.

TARGET SUBJECT POPULATION

Subjects will be aged ≥ 18 years with a body mass index ≥ 30 kg/m^2, with biopsy-confirmed NAFLD/NASH, and liver fibrosis stage F1, F2 or F3.

TREATMENT GROUPS AND REGIMENS

- **MEDI0382 300 µg:** MEDI0382 SC 50 µg once daily for 1 week, followed by 100 µg daily for 2 weeks, 200 µg daily for 2 weeks and 300 µg daily for 14 weeks (n = 24).
- **Placebo for MEDI0382 300 µg**: matched placebo SC once daily for 19 weeks (n = 12).
- **MEDI0382 600 µg**: MEDI0382 SC 50 µg once daily for 1 week, followed by 100 µg daily for 2 weeks, 200 µg daily for 2 weeks, 300 µg daily for 2 weeks, 400 µg daily for 2 weeks, 500 µg daily for 2 weeks and 600 µg daily for 8 weeks (n = 24).

  Placebo for MEDI0382 600 µg: matched placebo SC once daily for 19 weeks (n = 12).

STATISTICAL METHODS

Sample size: The primary objective of the study is safety, but sample size and power are calculated on efficacy endpoint HFF. Assuming 20% treatment difference on relative change in HFF with standard deviation (SD) = 20%, and assuming a 25% dropout rate, 24 subjects per group will provide about 83% power to detect a treatment difference between a MEDI0382 group and the placebo (alpha = 0.05, 2-sided). No multiplicity adjustment for alpha is planned.

Statistical analyses: The safety analyses will be based on the As-treated population. Treatment emergent adverse events will be summarized for incidence with number and percentage. Other safety data, such as vital signs, clinical laboratory data, and dECG will be summarized descriptively.

The pharmacodynamic analyses will be based on the Intent-to-treat population. For pharmacodynamic endpoints with continuous distribution, analysis of covariance (ANCOVA) adjusted for baseline value will be conducted.

Pharmacokinetic and immunogenicity analyses: Pharmacokinetic parameters such as, but not limited to, $C_{max,}$ $t_{max,}$ and AUC per group on the last day of dosing, may be estimated from plasma concentration-time data for MEDI0382 if data permit. Descriptive statistics will be generated for pharmacokinetic parameters for MEDI0382 in group. Additional summary statistics on predose concentrations and specific postdose concentrations may be derived, if data permits, from all groups. Subjects who have at least one measurable concentration time point of investigational product will be used for this analysis. Samples confirmed positive for ADA will be analyzed for antibody titer, ADA incidence rate and titer will be tabulated.

Interim analysis: An interim analysis is planned after approximately 39 subjects have completed approximately 19 weeks of treatment. The purpose of this interim analysis is to help inform further clinical development; no changes will be made to this study unless a safety signal is observed. The interim analysis results will not be provided to the investigator. The interim analysis will be described in the interim analysis charter.

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ABPM	ambulatory blood pressure monitoring
ADA	anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APRI	AST platelet ratio index
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUDIT	Alcohol Use Disorder Identification Test
BARD score	BMI, Ratio, Diabetes Score
BMI	body mass index
BP	blood pressure
CI	confidence interval
CLDQ-NASH	Chronic Liver Disease Questionnaire for non-alcoholic steatohepatitis
C_{max}	maximum observed plasma drug concentration
COVID-19	Coronavirus disease 19
CSA	clinical study agreement
CSR	clinical study report
dECG	digital electrocardiogram
DNL	de novo lipogenesis
DPP-4i	dipeptidyl peptidase-4 inhibitor
eCRF	electronic case report form
E-code	subject identification number
FAAN	Food Allergy and Anaphylaxis Network
FIB-4	fibrosis-4 score
FLI	fatty liver index
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GGT	gamma glutamyl transferase
HbA1c	hemoglobin A1c

Abbreviation or Specialized Term	Definition
HDLc	high density lipoprotein cholesterol
HFF	hepatic fat fraction
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IWRS	interactive web response system
LDLc	low density lipoprotein cholesterol
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MRI-PDFF	magnetic resonance imaging-proton density fat fraction
NAFLD	non-alcoholic fatty liver disease
NAS	NASH activity score
NASH	non-alcoholic steatohepatitis
NIAID	National Institute of Allergy and Infectious Diseases
NFS	NAFLD fibrosis score
NOAEL	no-observed-adverse-effect-level
PPAR-γ	peroxisome proliferator-activated receptor gamma
PRO	patient reported outcomes
RR	relative risk
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SF-36	Short-Form-36
SGLT-2	sodium-glucose co-transporter 2
T2DM	type 2 diabetes mellitus
TBL	total bilirubin
t_{max}	time to maximum observed plasma drug concentration
ULN	upper limit of normal
URC	Unblinded Review Committee
US FDA	United States Food and Drug Administration

Abbreviation or Specialized Term	Definition
USA	United States of America
w/v	weight per volume

1 INTRODUCTION

1.1 Disease Background

Non-alcoholic steatohepatitis (NASH) is part of the spectrum of liver diseases known as non-alcoholic fatty liver disease (NAFLD), ranging from simple steatosis or non-alcoholic fatty liver (NAFL) to NASH. NAFLD is the most common cause of chronic liver disease in western industrialized countries and has an estimated prevalence of approximately 6% to 35% worldwide (Bellentani, 2017; Younossi et al, 2016). NASH is the progressive form of the disease with a prevalence of approximately 2% to 3% of the general population, which can lead to cirrhosis and its complications, hepatocellular carcinoma, and end-stage liver disease (Bellentani et al, 2010). NASH is expected to become the leading cause for liver transplantation over the next decade, and is an important etiology driving the burden of hepatocellular carcinoma (Cholankeril et al, 2017; Pais et al, 2016; Wong et al, 2014). NASH is closely associated with metabolic risk factors including obesity, type 2 diabetes mellitus (T2DM), and dyslipidemia. Of particular relevance, epidemiological studies have demonstrated the prevalence of co-morbid obesity and T2DM in approximately 80% and 45% of patients with NASH, respectively (Younossi et al, 2016). Pathophysiologically, NASH is frequently associated with insulin resistance, leading to adipose tissue dysfunction and increased hepatic de novo lipogenesis (DNL). Therefore, it is believed that both increased adipose tissue lipolysis and hepatic DNL contribute to increased liver fat and formation of lipid metabolites causing lipotoxicity. Lipotoxicity, oxidative stress and mitochondrial dysfunction are believed to contribute to the hallmarks of NASH including signs of cell death or hepatocyte ballooning, lobular or portal inflammation and ultimately in some patients, liver fibrosis (Marra and Lotersztajn, 2013; Neuschwander-Tetri, 2017).

NASH is defined histologically as the combination of hepatic steatosis, inflammation and hepatocyte ballooning. Approximately 25% to 35% of patients with NASH develop liver fibrosis (Mishra and Younossi, 2012). The fibrosis stage (F1 to F4) is the most important prognostic factor in NASH correlating with liver-related outcomes and mortality (Angulo et al, 2015; Dulai et al, 2017). A number of factors have been shown to increase the risk of liver fibrosis progression to cirrhosis including presence of comorbid T2DM, increasing age, hypertension, and high body mass index (BMI) (Angulo, 2007).

There are currently no licensed pharmacological therapies for NASH, with lifestyle modifications being the mainstay of treatment. Many patients do not achieve or maintain dietary goals and weight loss. Consequently, the development of new therapies for NASH is an area of high unmet medical need, particularly given the expected increasing burden of this disease in parallel with the rising global epidemics of obesity and T2DM (Estes et al, 2018).

1.2 MEDI0382 Background

MEDI0382 is briefly described below. A detailed description of the chemistry, pharmacology, efficacy, and safety of MEDI0382 is provided in the Investigator's Brochure (IB).

Glucagon-like peptide-1 (GLP-1) receptor agonists are established treatments for T2DM that improve glycemic control, delay gastric emptying, and depress appetite leading to modest weight loss (typically 4% to 5.4% placebo-subtracted weight loss at 1 year) (Astrup et al, 2012). The strong association of NASH with the metabolic syndrome, particularly obesity and T2DM, has led to the investigation of GLP-1 agonists in this setting due to their positive effects on weight loss and insulin sensitivity.

In a metabolic sub-study of the multicenter, double-blind, randomized LEAN study, patients with NASH who were treated with the GLP-1 receptor agonist liraglutide 1.8 mg (Victoza®) for 12 weeks showed increased insulin sensitivity and metabolic improvement such as decreased levels of circulating non-esterified fatty acids and markers of adipose inflammation (Armstrong et al, 2014). In the main 48-week LEAN study of 52 patients with NASH, treatment with liraglutide 1.8 mg led to histological resolution of NASH in 9 (39%) patients who underwent end of treatment liver biopsy compared with 2 (9%) patients in the placebo group (4.3 relative risk [RR], 95% confidence interval [CI] 1.0, 17.7; p = 0.019) (Armstrong et al, 2016). Fewer patients in the liraglutide group versus the placebo group (9% versus 36%, respectively) had progression to liver fibrosis (0.2 RR, 95% CI 0.1, 1.0; p = 0.04).

MEDI0382 is an oxyntomodulin-like peptide with targeted GLP-1 and glucagon receptor activity that is under development for the treatment of overweight/obese patients with T2DM. The additional glucagon component has similar effects to GLP-1 on gastric emptying and appetite and has also been shown to promote increased energy expenditure (Habegger et al, 2013; Lynch et al, 2014). Oxyntomodulin, a naturally occurring peptide with GLP-1 and glucagon receptor co-agonist activity, has been shown to promote weight loss through effects on appetite and energy expenditure in obese humans (Wynne et al, 2006). In addition, co-infusion of GLP-1 and glucagon has demonstrated synergistic effects on reducing food intake and increasing energy expenditure in humans (Cegla et al, 2014). In a rodent model of NASH, the synthetic GLP-1 and glucagon receptor co-agonist G49 has been shown to improve the histological features of NASH following a methionine and choline-deficient diet (Valdecantos et al, 2017).

MEDI0382, through targeted GLP-1 and glucagon receptor activity, is therefore hypothesized to lead to histological resolution of NASH, along with providing beneficial effects on glucose and lipid metabolism.

1.3 Summary of Nonclinical Experience

Refer to the current MEDI0382 IB for a complete summary of non-clinical information.

A series of repeat-dose-toxicity studies that included a 6-month study in rat and a 9-month study in the cynomolgus monkey were performed. Consistent with GLP-1 receptor mono-agonists, MEDI0382 exposure in both rats and cynomolgus monkeys resulted in the anticipated pharmacologic effects on body weight (reduced gain, or loss), food consumption (sporadic reductions), water consumption (low throughout dosing periods), gastric emptying (delayed in rats), liver (changes indicative of an effect on energy homeostasis in both species), pancreas (hypercellularity of the pancreatic islets, acinar degranulation), adrenal glands (increased prominence of the zona glomerulosa), and lungs (increased macrophage number, rats only). Skin findings (dry scaling, flaky and occasionally reddened) noted in-life in high dose group female cynomolgus monkeys only, appeared to be recovering in the treatment-free phase of the 9-month toxicology study. Microscopically this correlated with dermal inflammation, hyperkeratosis and acanthosis in the affected females and in 1 male not previously showing this clinically. The onset of the clinical observations coincided with the intensive investigations conducted during Week 26 of the study, which included overnight housing of animals in metabolism cages that can be stressful to some animals. The skin changes observed are likely to be study conduct- and stress-related, with the secondary effects of MEDI0382-induced weight loss (greatest in females) potentially affecting skin condition in affected animals. MEDI0382 was not genotoxic and was not considered to be toxic to fertility or embryo fetal development in the rat and rabbit, with most findings generally being associated with maternal stress.

In 2 mouse models of NASH, wild type (C57BL6J) or genetically obese (Lep^{ob}/Lep^{ob}) mice fed a diet high in trans-fat, fructose, and cholesterol, had repeated subcutaneous (SC) once daily dosing of MEDI0382 (40 µg/kg or 111.84 µg/kg, respectively) for 6 weeks, that resulted in improvements in metabolism (reduced body weight, improved glucose tolerance), and liver enzymes, hepatic steatosis, and histological features of NASH compared with vehicle control(s). Both wild type and genetically obese mice treated with MEDI0382 had a statistically significant ($p < 0.05$) lower NASH activity score (NAS) compared with vehicle. The genetically obese mice treated with MEDI0382 had a statistically significant ($p < 0.05$) reduction in liver fibrosis compared with vehicle, which was supported by statistically significant reductions ($p < 0.05$) in plasma levels of the neoepitope of matrix metallopeptidase 9-mediated degraded type III collagen (C3M) and internal epitope in the 7S domain of type IV collagen (P4NP7S) biomarkers (as measured by collagen staining) compared with vehicle.

1.4 Summary of Clinical Experience

This is the first study with MEDI0382 in subjects with non-cirrhotic NAFLD/NASH with fibrosis stages F1, F2, or F3, however, seven clinical studies with MEDI0382 are complete and six ongoing including two studies with dosing up to 600 µg, one in obese subjects with T2DM and the other in subjects with chronic weight management or obesity (see current IB for details). Safety assessments for the completed studies show that the administration of

MEDI0382 was generally well tolerated, with more frequent, usually mild or moderate, gastrointestinal treatment emergent adverse events as expected from this drug class.

In the completed Phase 1/2a (Study D5670C00002) study conducted in 51 overweight and obese subjects with T2DM who received 41 days of placebo or MEDI0382 titrated up to a dose of 200 µg, a mean reduction from baseline in weight of −4.12% (90% CI −4.88, −3.36) was observed in MEDI0382-treated subjects versus −1.78% (90% CI −2.52, -1.03) in placebo, and a mean reduction from baseline in glucose area under curve for mixed meal test 4 hours (AUCMMT.4 h) of -32.78% (90% CI -36.98, -28.57) versus -10.16% (90% CI −14.10, -6.21) in placebo, $p < 0.0001$. The effects of MEDI0382 (at a dose of 200 µg, dose titrated from 100 µg) on hepatic fat content as measured by magnetic resonance imaging-proton density fat fraction (MRI-PDFF), was measured as an exploratory endpoint in this study, and demonstrated a significant reduction versus placebo ([*Absolute*: least squares [LS] mean change (90%CI): -5.98 (-7.67, -4.29) versus -3.17 (-4.68, -1.65), $p = 0.017$; *Relative*: LS mean change (90%CI): -39.12% (-49.11, -29.14) versus -19.51% (-28.49, -10.53), $p = 0.006$]) (Ambery et al, 2018).

1.5 Rationale for Conducting the Study

It has been previously shown that GLP-1 mono-agonists reduce liver fat and improve histological features of NASH (Armstrong et al, 2016; Petit et al, 2017). Given MEDI0382 has additional effects on glucagon that could lead to both a reduction in weight and may additionally lead to direct hepatic effects, it is anticipated that MEDI0382 use will lead to reduction of liver fat, liver stiffness and circulating markers of hepatocellular injury in this subject population. As outlined above, up to 6-week data demonstrating the safety and efficacy of MEDI0382 across numerous metabolic endpoints in overweight and obese T2DM populations in clinical settings (Study D5670C00002) have been collected. MEDI0382 (at a dose of 200 µg) was associated with significant reductions in liver fat, as assessed by MRI-PDFF after 41 days of treatment, in a subgroup within a Phase 1/2a study in overweight/obese subjects with T2DM (Study D5670C00002). However, we have no data on the effect of MEDI0382 on safety and measures of hepatic steatosis and inflammation in the target population of NAFLD/NASH with fibrosis (F1, F2, or F3). Furthermore, we have no data at doses greater than 200 µg in a population with NAFLD/NASH with fibrosis. Access to such data are necessary to support development and design of a longer term pivotal study in subjects with NASH with fibrosis, particularly as outlined in the recently released draft guidance from the United States Food and Drug Administration (US FDA) on non-cirrhotic NASH with fibrosis.

This will be the first study to investigate the effect of MEDI0382 in subjects with non-cirrhotic NAFLD/NASH with fibrosis (F1, F2, or F3). This proof of concept study will evaluate the safety, tolerability and pharmacodynamics of MEDI0382 in obese subjects with

biopsy-confirmed non-cirrhotic NAFLD/NASH with fibrosis, enabling us to define the short-term effects of MEDI0382 in the target population for this therapy. In turn, it is expected that data from the proposed study will support key considerations for safety, study design, dose selection, sample size estimation, development of endpoints and even regulatory discussions to enable larger longer studies of MEDI0382 in a population with non-cirrhotic NAFLD/NASH with fibrosis.

1.6 Benefit-risk and Ethical Assessment

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation (ICH)/Good Clinical Practice (GCP), and applicable regulatory requirements.

This is the first clinical study in which MEDI0382 will be used in subjects with NASH and is expected to lead to improvement of NASH based on non-invasive parameters, along with significant weight reduction.

Identified and potential risks for MEDI0382 are based on available published data for other GLP-1 receptor mono-agonists and glucagon receptor mono-agonists, as well as clinical and non-clinical data for MEDI0382. Identified risks/adverse drug reactions for MEDI0382 are nausea, vomiting, injection site reactions and increased heart rate. The current IB should be consulted for potential risks; for MEDI0382 these include, alterations in blood pressure (BP), QT-interval prolongation, anaphylactic-type reactions, skin rash, pancreatitis, pancreatic carcinoma, thyroid cancer, hypoglycemia (with sulfonylurea/insulin) and diabetic ketoacidosis (following insulin reduction). The study design aims to minimize potential risks to subjects participating in this study based on the proposed inclusion/exclusion criteria, safety monitoring, and up-titration dosing schedule. Additionally, subjects will be monitored throughout the study for signs, symptoms, and/or laboratory analyses suggestive of hepatic decompensation. Subjects with hepatic decompensation will be excluded from participation in this study (Section 5.2) and will be treated immediately according to standard of care. Subjects will be given appropriate training in SC injection administration.

More detailed information about the known and expected benefits and identified and potential risks and expected adverse events (AEs) of MEDI0382 may be found in the current IB.

1.7 Research Hypotheses

1.7.1 Primary Hypothesis

MEDI0382 will have an acceptable safety (including hepatic safety) and tolerability profile in subjects with NAFLD/NASH.

1.7.2 Secondary Hypotheses

Treatment with any one dose of MEDI0382 tested will lead to a reduction in hepatic fat in subjects with NAFLD/NASH.

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective and Associated Endpoint

Table 1 Primary Objective and Associated Endpoint

Type	Objective	Endpoint
Safety	To assess the safety (including hepatic safety) and tolerability of MEDI0382 compared with placebo	• Incidences of treatment emergent adverse events and serious adverse events through the end of the follow-up period.

2.2 Secondary Objectives and Associated Endpoints

Table 2 Secondary Objectives and Associated Endpoints

Type	Objective	Endpoint
Pharmacodynamic effects	To assess the effect of MEDI0382 on relative and absolute change in hepatic fat as assessed by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) compared with placebo	• Percent change from baseline in hepatic fat fraction (HFF) at Week 19 • Absolute change from baseline to Week 19 in HFF
[redacted]	[redacted]	CCI [redacted]
Pharmacodynamic effects	To assess the effect of MEDI0382 on circulating markers of hepatic inflammation compared with placebo	Change and percent change from baseline to Week 19 in: • alanine aminotransferase (ALT) • aspartate aminotransferase (AST) • gamma glutamyl transferase (GGT)
Pharmacodynamic effects	To assess the effect of MEDI0382 on body weight and body mass index (BMI) compared with placebo	• Change and percent change from baseline to Week 19 in body weight and BMI.
Dose response	To assess the dose response of MEDI0382 on pharmacodynamic parameters	• HFF, body weight, safety, other imaging parameters, parameters of hepatic inflammation
Immunogenicity	To evaluate the immunogenicity of MEDI0382	• Development of anti-drug antibodies (ADA) and titer (if subjects are ADA positive) during treatment and follow-up

2.3 Exploratory Objectives and Associated Endpoints

Table 3 Exploratory Objectives and Associated Endpoints

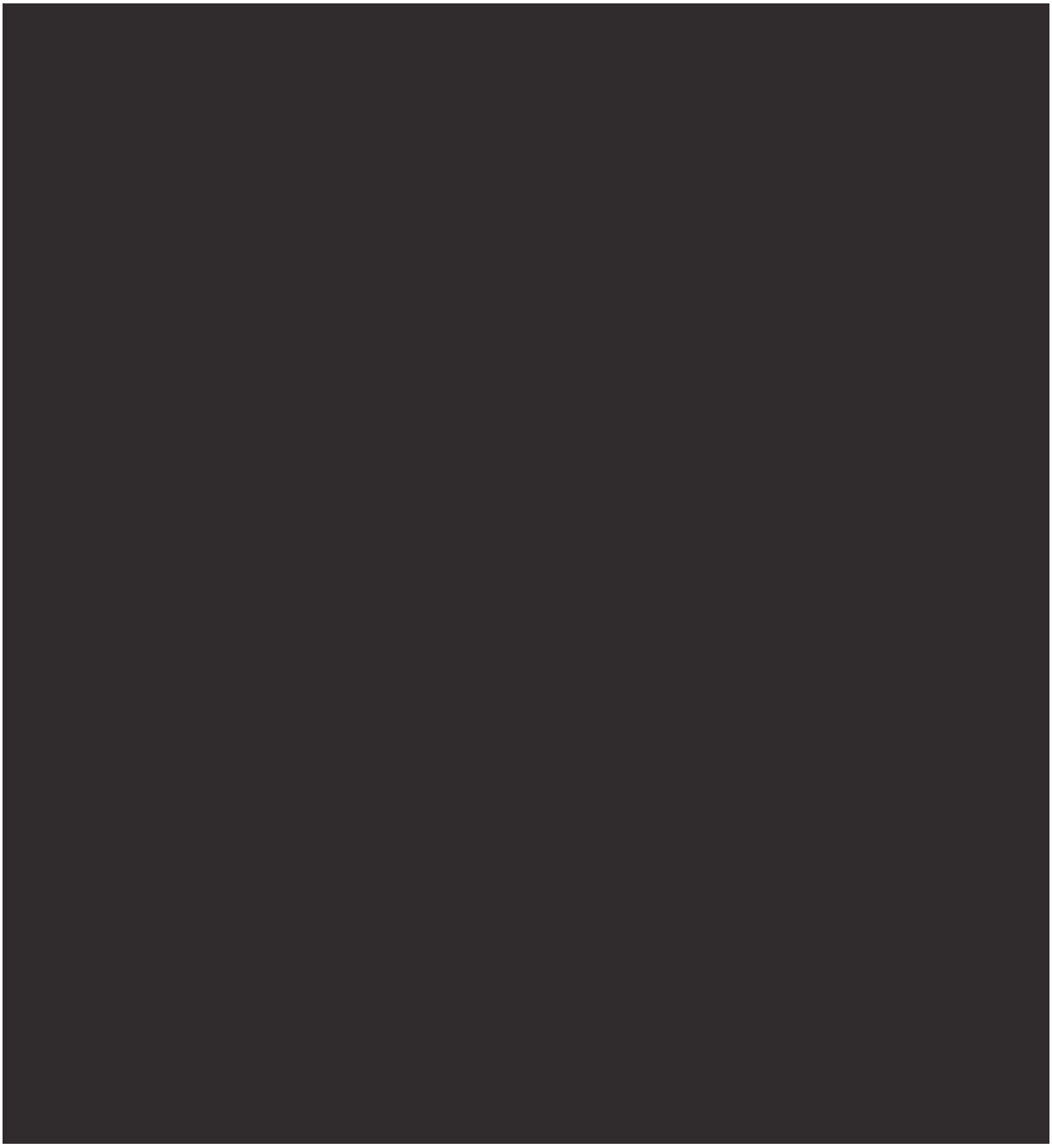


Table 3 Exploratory Objectives and Associated Endpoints

3 STUDY DESIGN

3.1 Description of the Study

3.1.1 Overview

This is a randomized, double-blind, placebo-controlled study to evaluate the safety (including hepatic safety), tolerability and pharmacodynamic effects of two dose levels of MEDI0382 in obese subjects with NAFLD/NASH. The subjects will have biopsy-confirmed NAFLD/NASH with liver fibrosis stages F1, F2 or F3. Approximately 72 subjects will be randomized across multiple study sites.

Subjects will be recruited in parallel and randomized using a 2:1:2:1 ratio:

- **MEDI0382 300 µg:** MEDI0382 SC 50 µg once daily for 1 week, followed by 100 µg daily for 2 weeks, 200 µg daily for 2 weeks and 300 µg daily for 14 weeks (n = 24).
- **Placebo for MEDI0382 300 µg**: matched placebo SC once daily for 19 weeks (n = 12).
- **MEDI0382 600 µg**: MEDI0382 SC 50 µg once daily for 1 week, followed by 100 µg daily for 2 weeks, 200 µg daily for 2 weeks, 300 µg daily for 2 weeks, 400 µg daily for 2 weeks, 500 µg daily for 2 weeks and 600 µg daily for 8 weeks (n = 24).

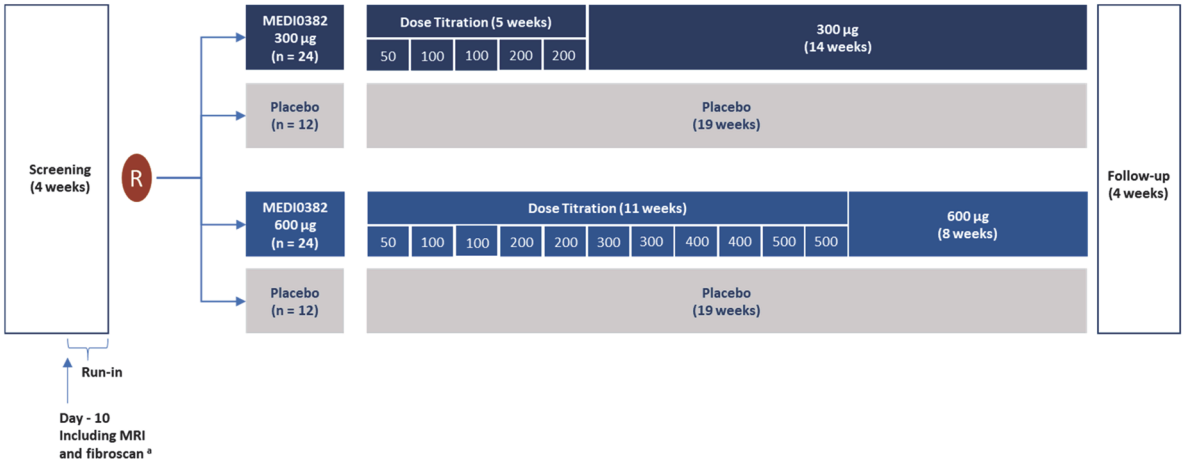
! **Placebo for MEDI0382 600 µg**: matched placebo SC once daily for 19 weeks (n = 12).

Subjects will be in the study for approximately 27 weeks (189 days), including a screening period of up to 4 weeks, a 19-week treatment period, and a 4-week safety follow-up period (Figure 1).

During the screening period, baseline circulating markers (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma glutamyl transferase [GGT]) will be obtained. Subjects will return to site for study procedures at regular intervals, including the collection of blood sampling for serum biomarkers and pharmacokinetics, and MRI (including MRI-PDFF) when applicable (refer to the schedule of study procedures).

To help inform further clinical development, once approximately 39 subjects have completed approximately 19 weeks of treatment an interim analysis is planned. The interim analysis results will not be provided to the investigator. The interim analysis will be described in the interim analysis charter.

Figure 1 Study Flow Diagram



MRI = magnetic resonance imaging; PDFF = proton density fat fraction; R = randomization

[a] Subjects with MRI (including MRI-PDFF) and fibroscan assessments performed within 60 days prior to screening do not need to undergo these assessments.

3.1.2 Treatment Regimen

Subjects randomized to placebo will receive matched placebo for 19 weeks.

Dose Up-titration Period

During the dose up-titration period, subjects randomized to receive MEDI0382 will titrate to the top dose in each group as follows:

MEDI0382 300 µg (5 weeks)

- 50 µg for 1 week (7 days)
- 100 µg for 2 weeks (14 days)
- 200 µg for 2 weeks (14 days)

MEDI0382 600 µg (11 weeks)

- 50 µg for 1 week (7 days)
- 100 µg for 2 weeks (14 days)
- 200 µg for 2 weeks (14 days)
- 300 µg for 2 weeks (14 days)
- 400 µg for 2 weeks (14 days)
- 500 µg for 2 weeks (14 days)

Subjects may travel to the site for daily visits during Week 1 or alternatively should be given the option to stay overnight locally, if this is more convenient.

Maintenance Treatment Period

During the maintenance treatment period, subjects randomized to receive MEDI0382 will titrate to the maintenance dose and continue with this dose to the end of the period:

MEDI0382 300 µg

- 300 µg for 14 weeks

MEDI0382 600 µg

- 600 µg for 8 weeks

3.1.3 Management of Study Medication Related Toxicities

3.1.3.1 Tolerability

To help prevent the occurrence of nausea and vomiting, prior to receiving investigational product, subjects will be counselled about meal size and eating habits. This advice should be re-iterated should symptoms occur once investigational product is initiated. In the event that symptoms do not improve, subjects should be offered anti-emetic therapy in accordance with institutional and local practice guidelines as long as medications that are prokinetic agents such as domperidone or metoclopramide are avoided.

MEDI0382 600 μg group only: in the event that a subject is unable to tolerate the investigational product following up-titration to 600 μg at Week 12, down-titration may be considered to the 500 μg dose level. If more than two subjects in the first eight subjects receiving 600 μg drop out or down-titrate to 500 μg, due to inability to tolerate the 600 μg dose, the remaining subjects in MEDI0382 600 μg group will not be up-titrated beyond the 500 μg dose level.

Investigators should monitor subjects with vomiting for signs of hypovolemia. Subjects with impaired renal function could be extra sensitive to hypovolemia. Such subjects should be informed about the importance of adequate hydration in case of nausea and vomiting. These subjects should also undergo additional laboratory testing for potential creatinine increases, as appropriate.

3.1.3.2 Hypoglycemia

Spontaneous and clinically significant hypoglycemia has not been experienced in completed studies with MEDI0382 up to a dose of 300 μg alongside metformin treatment.

Self-monitored plasma glucose or blood glucose readings and hypoglycemic events will be reviewed and managed by the investigator as per local standards of care. Subjects with T2DM will be provided with glucose meters and should be advised to use the glucose meter to check their capillary blood glucose level as per their usual schedule and if they have symptoms of hypoglycemia (hunger, dizziness, shaking, sweating, etc) or feel unwell. Any blood glucose level < 3.0 mmol/L (54 mg/dL) is considered as clinically significant hypoglycemia regardless of symptoms or not and should be reported by investigators as an AE.

In the event of a severe hypoglycemic episode in a subject with T2DM taking oral antidiabetic agents, dose reduction of such medication should be considered. In the event that no dose reduction of oral anti-diabetic agents can be undertaken, the subject may be withdrawn from treatment following discussion by the investigator with the medical monitor. Subjects should not be discontinued from treatment based on single episodes of hypoglycemia or symptoms of hypoglycemia unless clinically indicated. The assessment of a single fingerstick or local

laboratory glucose value should not be the sole assessment used to determine subject discontinuation due to hypoglycemia.

The definition of a severe hypoglycemic event is as follows:

"Severe hypoglycemia is an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration" (Seaquist et al, 2013).

3.1.3.3 Persistent Hyperglycemia

Rescue therapy will be considered for any subject with persistent hyperglycemia. Self-monitored plasma glucose or blood glucose readings will be collected and reviewed by the investigator. Rescue therapy with add-on insulin is the preferred option for rescue therapy, but additional drug classes are permitted. In addition, the dose of metformin may be increased. Any change in anti-diabetic medications must be recorded in the electronic case report form (eCRF). It is advisable to avoid dipeptidyl peptidase-4 inhibitor (DPP-4i)-based treatments for rescue therapy for hyperglycemia. In the event of a need for rescue therapy for hyperglycemia, alternative options should be considered. Rescue therapy with any GLP-1 receptor agonist, or peroxisome proliferator-activated receptor gamma (PPAR-γ) agonist-based intervention is prohibited.

3.2 Rationale for Dose, Population, and Endpoints

3.2.1 Dose Rationale

No clinical studies with MEDI0382 have been performed to date in subjects with non-cirrhotic NAFLD/NASH with fibrosis; however, MEDI0382 has been studied in overweight/obese subjects with T2DM (Section 1.4). Given the pathophysiological overlap of subjects with T2DM and NASH (~80% of NASH patients are obese, and approximately 50% have T2DM [Younossi et al, 2016]), the data for subjects with T2DM are relevant for subjects with NASH.

Reductions in weight have been shown to be related to histological changes in NASH and liver fibrosis (Vilar-Gomez et al, 2015). Therefore, the effect of body weight change is particularly relevant, as it provides a link between the two indications with respect to dose response.

Current experience with marketed GLP-1 receptor agonists suggests that higher doses of GLP-1 receptor agonist therapy may be associated with greater durability of weight loss, and there is a known association between degree of weight loss and improvement in hepatic fat as well as histological features of NASH with fibrosis. Furthermore, data from a bariatric surgery study indicate that greater weight loss is associated with greater improvements in steatosis and

even hepatic inflammation. Taken together, since weight loss is at least in part responsible for the anticipated improvements in NAFLD/NASH, it is important to establish whether near maximal GLP-1/glucagon dual agonism at higher doses up to and beyond those studied exhibits a pharmacodynamic profile that recapitulates or is even perhaps superior to that reported with GLP-1 receptor agonists, and to dissect out the weight loss-dependent and independent effect on hepatic fat in patients with non-cirrhotic NAFLD/NASH with fibrosis. MEDI0382 at 200 µg (Study D5670C00002) was associated with significant reductions in liver fat and improvement in transaminase levels in a group of overweight/obese subjects with T2DM. Assessment of safety and tolerability of doses of MEDI0382 higher than 300 µg and up to 600 µg in an obese population is currently ongoing (Study D5672C00001). Taken together, the planned active doses for the current proposed study in subjects with non-cirrhotic NAFLD/NASH with fibrosis will include a 600-µg dose arm, determined as the maximal tolerated dose in Cohort 1 of the ongoing titration Study D5672C00001 in 12 obese subjects treated with MEDI0382 for maximum 2 weeks on stable dose. Review of preliminary safety data revealed no new safety concerns with the data supportive of the use of such doses in similar settings. Therefore, the current study proposes to assess the effects of MEDI0382 at the 600 µg dose in a population with biopsy-confirmed non-cirrhotic NAFLD/NASH with fibrosis (F1, F2, F3) (with the opportunity to down-titrate to 500 µg for the entire group based on tolerability in the first 8 subjects (see Section 3.1.3). However, there remains a risk that doses higher than 300 µg may not be tolerated in this population. In order to mitigate such risk, and to be able to gain meaningful information from this critical study, evaluation of the effects of MEDI0382 at the 300 µg dose in a second group of subjects with non-cirrhotic NAFLD/NASH with fibrosis (F1, F2, or F3) will be performed. Considering the separation between the two dose levels in terms of plasma exposure, such a strategy will also add considerable value for optimization of dose selection for planned pivotal studies for the MEDI0382 NASH program.

The no-observed-adverse-effect-level (NOAEL) of 90 µg/kg/day was based on findings in the 9-month, daily repeat-dose SC toxicology study in the cynomolgus monkey. These were considered to be consistent with pharmacology-mediated induction of weight loss/lower weight gain, reversible changes in the pancreas (acinar degranulation and hypercellularity of the pancreatic islets), and changes in energy utilization and associated metabolic stress (minor changes in blood chemistry parameters, lower thymus weights). Treatment was also associated with changes in the skin (dermal inflammation, acanthosis and hyperkeratosis) in 3 of 6 female cynomolgus monkeys dosed.

While the NOAEL determined in the rat 6-month, daily repeat-dose SC toxicology study (ie, 7.5 µg/kg/day) was lower than that in the cynomolgus monkey, this was driven primarily by the findings in the thyroid gland (C-cell hyperplasia, adenoma, and carcinoma) that were considered, in this species, to be adverse. This is a known class effect with GLP-1 receptor agonists that is considered rodent specific and of unknown relevance to humans (Center for

Drug Evaluation and Research, 2005). Therefore, cynomolgus monkey, and the toxicity profile of MEDI0382 generated in that species, are the most appropriate non-clinical species to use for clinical risk assessment and the setting of safety margins.

Table 4 illustrates the main proposed clinical dose periods and estimated safety margins over the predicted maximum observed concentration (C_{max}) and AUC in humans for this repeat-dose study and the observed C_{max} and AUC at the NOAEL in the 9-month repeat-dose toxicity study in cynomolgus monkeys. The steady state C_{max} and AUC-based safety margins at the maximum proposed human dose of 600 µg after up-titration steps based on cynomolgus monkey NOAEL (90 µg/kg/day) are 12-fold and 8-fold, respectively, which indicates that the exposure is anticipated to be lower in humans to that determined in monkeys at the NOAEL.

Table 4 Proposed Study Doses and Predicted Safety Margins Based on Safety Data From the Cynomolgus Monkey

Human Dose (µg)	Predicted Median Human Exposure at steady state		Safety Margin Over Cynomolgus Monkey Exposure at NOAEL[a] at Day 273	
	AUC_{tau} (ng•hr/mL)	C_{max} (ng/mL)	AUC	C_{max}
50	51	3.4	82	119
100	84	5.5	50	74
200	160	10.6	26	38
300	249	17	17	25
600	498	33	8	12

AUC = area under the concentration-time curve; BMI = body mass index; C_{max} = maximum observed concentration; NOAEL = no-observed-adverse-effect level.

Note: The information in this table is based on BMI of 35 kg/m^2.

[a] NOAEL = 90 µg/kg/day

3.2.2 Rationale for Study Population

Obese subjects with biopsy-confirmed non-cirrhotic NAFLD/NASH with fibrosis and with or without T2DM, will be recruited, as such subjects would gain the most benefit from treatment with MEDI0382, rather than healthy subjects who would not see disease benefits. Subjects with non-cirrhotic NAFLD/NASH with fibrosis stage F1, F2 or F3 (inclusive) will be recruited. In order to ensure a balance of subjects with early and advanced fibrosis, the number of subjects with F1 fibrosis will be capped at 25% in the study. Subjects with F4 fibrosis (cirrhosis) will not be included because histological progression is less relevant in these subjects, where the therapeutic emphasis is more on the reduction of the physiological abnormalities (e.g., elevated portal pressure). Obese subjects are included because excess weight is associated with the development of NASH and MEDI0382 is expected to promote weight loss.

3.2.3 Rationale for Endpoint(s)

Rationale for Primary Endpoint

1 The current study will evaluate the overall safety (including hepatic safety) and tolerability in the setting of multiple dosing of MEDI0382 (up to 600 µg) in a population with biopsy-confirmed non-cirrhotic NAFLD/NASH with fibrosis.

Rationale for Secondary Endpoints

1 Improvements in hepatic steatosis have been associated with a therapeutic response in the resolution of NASH. MRI-PDFF has been demonstrated to be as sensitive as histology for detecting changes in whole liver fat content in natural history and therapeutic studies (Meisamy et al, 2011). Furthermore, MRI-PDFF is a non-invasive assessment with less risk to the subject and is less operator-dependent than other methodologies. A relative reduction of liver fat content by about 29% has been shown to be associated with histologic improvements in NASH (Patel et al, 2016). Use of the GLP-1 and glucagon co-agonist MEDI0382 was associated with significant reductions in liver fat in a group of overweight/obese subjects with T2DM in the setting of a subgroup within a Phase 1/2a study (Study D5670C00002). Therefore, it is reasonable to propose and anticipate a clinically relevant and statistically significant reduction of hepatic fat measured by MRI-PDFF in a population of biopsy-confirmed non-cirrhotic NAFLD/NASH with fibrosis. However, the population proposed for the current study is expected to have an admixture of pathologic features of NAFLD, NASH, and fibrosis, with varying degrees of improvement in each of these pathophysiologic features and varying time courses for such improvement in response to MEDI0382. Since steatosis will be a part of the pathophysiologic picture, but may not be the dominant pathologic feature, it is expected that we will observe a significant and clinically relevant change in HFF in the current study, but of a magnitude that may be less robust than in a population with steatosis alone. Furthermore, it is anticipated that prolonged treatment should lead to greater reductions in HFF in response to MEDI0382. Taken together, we anticipate a difference from placebo in the relative reduction from baseline in HFF in response to at least one dose of MEDI0382 tested in the current study. It is reasonable to propose that such a change in steatosis along with decreases in inflammation and NASH disease activity following prolonged treatment should position MEDI0382 as a viable treatment option for subjects with biopsy-confirmed non-cirrhotic NASH with fibrosis.
2 Hepatic fat fraction: Improvements in hepatic steatosis have been associated with a therapeutic response in the resolution of NASH. MRI-PDFF has been demonstrated to be as sensitive as histology for detecting changes in whole liver fat content in natural history and therapeutic studies (Meisamy et al, 2011). Furthermore, MRI-PDFF is a non-invasive assessment with less risk to the subject and is less operator-dependent than other methodologies. A reduction of absolute liver fat content by at least 5% has been shown to be associated with histologic improvements in NASH (Patel et al, 2016). Use of the GLP-1 and glucagon co-agonist MEDI0382 was associated with significant reductions in liver fat in a group of overweight/obese subjects with T2DM in the setting of a subgroup within a Phase 1/2a study (Study D5670C00002). Therefore, it is reasonable to propose

and anticipate a reduction of absolute hepatic fat measured by MRI-PDFF in a population of biopsy-confirmed non-cirrhotic NAFLD/NASH with fibrosis.

3 Markers of hepatic inflammation: Changes in circulating levels of transaminases such as ALT, AST, and GGT are considered in part to represent changes in hepatic inflammatory activity. The current study will measure changes in circulating levels of transaminases as indices of hepatic inflammation in a population with non-cirrhotic NASH with fibrosis.

4 Body weight and BMI: Excess body weight is associated with the development of NASH. Cotadutide is expected to promote weight loss and a reduction in body weight is potentially an indicator of therapeutic response.

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

In total, 72 subjects are planned for inclusion in this study; 24 subjects will be randomized to each of the MEDI0382 groups (300 and 600 μg); and 12 subjects will be randomized to each of the corresponding placebo groups.

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1 Provision of informed consent (with the exception of consent for future genetic and non-genetic research) prior to performing any study-specific procedures, including screening evaluations.

2 Subjects aged ≥ 18 years at the time of consent.

3 BMI ≥ 30 kg/m^2 at screening.

4 Hemoglobin A1c (HbA1c) ≤ 9.5% (inclusive) at screening if T2DM present, managed by either diet and/or a stable dose of metformin, sodium-glucose co-transporter 2 (SGLT-2) inhibitors, sulphonylureas or acarbose (ie, no major dose adjustments in prior 3 months to screening).

5 Definitive NAFLD/NASH with NAS ≥ 4 with ≥ 1 in each component (ie, steatosis, lobular inflammation and ballooning), as diagnosed by liver biopsy within 6 months of screening with liver fibrosis stage F1, F2 or F3. The number of subjects with F1 will be capped at 25% in the study.

6 Evidence of hepatic steatosis or liver fat (≥ 10%) by MRI-PDFF. Subjects with imaging performed within 60 days prior to screening do not need to repeat this assessment at Visit 2 (Day -10).

7 Women of childbearing potential:

(a) Who are sexually active with a non-sterilized male partner must have used at least one highly effective method of contraception (see Section Appendix A for definition of females of childbearing potential and for a description of highly effective methods

of contraception) from screening, and must agree to continue using such precautions through to the end of the study. It is strongly recommended for the male partner of a female subject to also use male condom plus spermicide throughout this period. Cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

(b) Must have a negative urine pregnancy test within 72 hours prior to the first dose of investigational product; and not be breastfeeding.

4.1.3 Exclusion Criteria

1 History of, or any existing condition that, in the opinion of the investigator, would interfere with evaluation of the investigational product, put the subject at risk, influence the subject's ability to participate or affect the interpretation of the results of the study.

2 Liver disease of other etiologies (e.g., alcoholic steatohepatitis; drug-induced, viral, or autoimmune hepatitis; primary biliary cirrhosis; primary sclerosing cholangitis; hemochromatosis; alpha 1 antitrypsin deficiency; Wilson's disease) including positive results for hepatitis B surface antigen (HBsAg) or hepatitis C antibody tests (anti-HCV).

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

4 Prior or planned liver transplantation.

5 Alcohol consumption > 21 units of alcohol per week for males and > 14 units per week for females on average over a two-year time frame prior to baseline biopsy.

6 Evidence of alcohol dependence as assessed by the Alcohol Use Disorder Identification Test (AUDIT) questionnaire at screening (Appendix F and Appendix G).

7 A history of type 1 diabetes mellitus (T1DM), a history of diabetic ketoacidosis or current use of insulin-based therapies.

8 Clinically significant inflammatory bowel disease or other severe disease or surgery affecting the upper gastrointestinal tract (including bariatric surgery) which may affect gastric emptying or could affect the interpretation of safety and tolerability data.

9 Physician-diagnosed diabetic subjects with clinically significant gastroparesis (as judged by the investigator) or those treated for gastroparesis within 6 months prior to screening.

10 History of > 5 kg weight loss in the last 6 months prior to screening or recent (within 3 months of screening) use of drugs approved for weight loss (e.g., orlistat, bupropion/naltrexone, phentermine-topiramate, phentermine, lorcaserin), as well as those drugs used off-label.

11 Clinically significant cardiovascular or cerebrovascular disease within the past 3 months, including but not limited to, myocardial infarction, acute coronary syndrome or stroke, or subjects who have undergone percutaneous coronary intervention or a coronary artery bypass graft within the past 6 months or who are due to undergo these procedures at the time of screening.

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

13 History of neoplastic disease within 5 years prior to screening, except for adequately treated basal cell, squamous cell skin cancer, or in situ cervical cancer.

14 History of substance dependence or a positive screen for drugs of abuse, likely to impact subject safety or compliance with study procedures, at the discretion of the Investigator.

15 History of psychosis or bipolar disorder. History of major depressive disorder within the past year with the subject being clinically unstable, or any history of suicide attempt or history of suicidal ideation within the past year.

16 Recent (within 3 months of baseline biopsy) use of therapies associated with development of NAFLD (e.g., systemic corticosteroids, methotrexate, tamoxifen, amiodarone, or long-term use of tetracyclines).

17 Recent (within 3 months of baseline biopsy) use of obeticholic acid or other therapy under investigation for NASH.

18 High dose vitamin E (> 400 IU) unless on a stable dose for at least 1 year prior to the baseline biopsy, and not initiated after the biopsy was taken.

19 Recent (within 3 months of baseline biopsy) use of GLP-1 receptor agonist or GLP-1 receptor agonist containing therapies.

20 Any subject who has received another investigational product as part of a clinical study within the last 30 days or 5 half-lives of the therapy (whichever is longer) at the time of screening. Any prior exposure to MEDI0382 is not permitted.

21 Concurrent participation in another interventional study of any kind or repeat randomization in this study.

22 Severe allergy/hypersensitivity to any of the proposed study treatments or excipients.

23 Contra-indication to MRI: such as subjects with pacemakers, metallic cardiac valves, magnetic material such as surgical clips, implanted electronic infusion pumps or other conditions that would preclude proximity to a strong magnetic field; subjects with history of extreme claustrophobia or subject cannot fit inside the MR scanner cavity.

24 History of acute pancreatitis or current chronic pancreatitis. Subjects with serum triglyceride concentrations above 1000 mg/dL (11 mmol/L) at screening, as this can precipitate acute pancreatitis.

25 Abnormal laboratory values including any of the following:

(a) AST or ALT > 5 × upper limit of normal (ULN).

(b) Impaired renal function defined as estimated glomerular filtration rate (eGFR) ≤ 30 mL/minute/1.73 m^2 at screening (estimated according to chronic kidney disease epidemiology collaboration [CKD-EPI]).

(c) Albumin < 35 g/L.

(d) International normalized ratio (INR) > 1.3.

(e) Total Bilirubin (TBL) > 25 μmol/L in the absence of known Gilbert's disease.

(f) Platelets < 140-150,000/mm^3.

(g) Any other clinically significant abnormalities in clinical chemistry, hematology, or urinalysis results as judged by the investigator.

26 Severely uncontrolled hypertension defined as systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 110 mmHg on the average of 2 seated measurements after being at rest for at least 10 minutes at screening or randomization.

27 Basal calcitonin level > 50 ng/L at screening, or history/family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 (MEN 2).

28 Hemoglobinopathy, hemolytic anemia, or chronic anemia (hemoglobin concentration < 11.5 g/dL [115 g/L] for male subjects or < 10.5 g/dL [105 g/L] for female subjects) at screening, or any other condition known to interfere with interpretation of HbA1c measurements

29 Any positive results for human immunodeficiency virus (HIV) infection.

30 Any AstraZeneca, MedImmune, or study site employee, or close relatives of any of the aforementioned employees.

31 Females who are pregnant or lactating.

Subjects may be re-screened once if the reason for screen failure was transient (including but not limited to study-supplied equipment failure or unforeseen personal events that mandate missed screening visits).

4.1.4 Subject Enrollment and Randomization

Study participation begins (ie, a subject is "enrolled") once written informed consent is obtained. Once informed consent is obtained, a subject identification (E-code) number will be assigned by a central system (e.g., an interactive web response system, IWRS), and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The E-code will be used to identify the subject during the screening process and throughout study participation, if applicable.

A master log of all consented subjects will be maintained at the site and will document all screening failures (ie, subjects who are consented but do not meet study eligibility criteria and are not randomized), including the reason(s) for screening failure.

Subjects who fail to meet the inclusion/exclusion criteria (ie, screening failures) should not be randomized or receive investigational product.

4.1.5 Screen Failures

Screen failures are defined as subjects who signed the informed consent form (ICF) to participate in the clinical study but are not subsequently randomized into the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened one time if they fulfil the inclusion/exclusion criteria then. The subject should sign a new informed consent if rescreened. The same E-code will be assigned for the rescreened subject.

These subjects should have the reason for screen failure recorded in the eCRF.

4.1.6 Withdrawal from the Study

Subjects are free to withdraw their consent to participate in the study (investigational product and assessments) at any time, without prejudice to further treatment. Subjects who withdraw consent will be asked about the reason(s) and the presence of any adverse events (AEs).

Subjects who are permanently discontinued from receiving investigational product will be recommended to continue the study and follow the original visit schedule without taking investigational product. If a subject discontinues from the investigational product, he or she should be asked, at the discretion of the treating physician, to return to the study site for the Early Discontinuation Visit (see Table 8). Where possible, the Early Discontinuation Visit should be within 7 days from last investigational product dose, unless consent is withdrawn from further study participation, or the subject is lost to follow-up (see Section 4.1.7). Subjects attending an Early Discontinuation Visit should also be asked to return 28 days (±3 days) from the last investigational product dose for follow-up assessments (see Table 8) unless they are unable or unwilling to return. If the subject continues in the study, after the Early Discontinuation Visit, the next visits should be planned in accordance to the original visit schedule. However, only 3 MRIs should be completed during the treatment period, for subjects discontinuing after Week 12 but before Week 19, the last MRI will be performed at the Early Discontinuation Visit. Any subject who has been randomized into the study will only have 3 MRIs performed during the treatment period. In all instances, adverse events will be followed up and all study medications should be returned by the subject.

If a subject withdraws from further participation in the study, then no further study visits or data collection should take place.

If a subject withdraws from the study, then his/her enrollment/randomization code cannot be reused. Withdrawn subjects will not be replaced.

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of the treatment must be documented.

4.1.7 Discontinuation of Investigational Product

An **individual subject** will not receive any further investigational product if any of the following occur in the subject in question:

1 Withdrawal of consent from further treatment with investigational product.
2 Lost to follow-up.
3 An AE that, in the opinion of the investigator or the sponsor, warrants discontinuation of further dosing.

4 Subject is determined to have met one or more of the exclusion criteria or failed to meet all of the inclusion criteria for study participation prior to start of study treatment but was entered into the study regardless.
5 Subject non-compliance that, in the opinion of the investigator or sponsor, warrants withdrawal (e.g., refusal to adhere to scheduled visits).
6 Pregnancy in a female subject.
7 Liver function tests meeting any of the following criteria:
   (a) ALT and/or AST are > 3 × ULN and TBL > 2 × ULN
   (b) ALT and/or AST are > 5 × ULN for ≥ 4 consecutive days, at any time after the initial confirmatory result in subjects with normal baseline values.
   (c) ALT and/or AST > 8 × ULN
   (d) New onset jaundice that is not explained by Gilbert's irrespective of other liver biochemistries
   (e) Albumin < 28 g/L
   (f) INR > 2
8 Acute viral hepatitis.
9 Symptoms or signs of cirrhosis and/or hepatic decompensation (e.g., ascites, variceal bleeding, hepatic encephalopathy).
10 Acute pancreatitis.

Subjects who are permanently discontinued from receiving investigational product will be recommended to continue the study and follow the original visit schedule without taking investigational product. If a subject discontinues from the investigational product, he or she should be asked, at the discretion of the treating physician, to return to the study site for the Early Discontinuation Visit (see Table 8). Where possible, the Early Discontinuation Visit should be within 7 days from last investigational product dose, unless consent is withdrawn from further study participation, or the subject is lost to follow-up. Subjects attending an Early Discontinuation Visit should also be asked to return 28 days (±3 days) from the last investigational product dose for follow-up assessments (see Table 8) unless they are unable or unwilling to return. If the subject continues in the study, after the Early Discontinuation Visit, the next visits should be planned in accordance to the original visit schedule. However, only 3 MRIs should be completed during the treatment period, for subjects discontinuing after Week 12 but before Week 19, the last MRI will be performed at the Early Discontinuation Visit. Any subject who has been randomized into the study will only have 3 MRIs performed during the treatment period.

4.1.8 Study Stopping Criteria

The study may be stopped if, in the judgement of MedImmune, study subjects are placed at undue risk because of clinically significant safety findings. The following criteria should be fulfilled:

- Meet individual stopping criteria or are otherwise considered significant
- Are assessed as causally related to investigational product
- Are not considered to be consistent with continuation of the study.

For the individual subject, all data available for the subject at the time of discontinuation or follow up must be recorded in the eCRF regardless of the reason for termination. All reasons for discontinuation of treatment must be documented.

In terminating the study, the sponsor will ensure that adequate consideration is given to the protection of the subjects' interests.

4.1.9 Replacement of Subjects

Subjects will not be replaced.

4.1.10 Withdrawal of Informed Consent for Data and Biological Samples

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

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

As collection of the biological samples is an integral part of the study, then the subject is withdrawn from further study participation.

The Principal Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to MedImmune.
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented.
- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented, and the signed document returned to the study site.
- Ensures that the subject and MedImmune are informed about the sample disposal.

MedImmune ensures the organizations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

4.2 Schedule of Study Procedures

Whenever vital signs, 12-lead digital electrocardiogram (dECG), and blood draws are scheduled for the same nominal time, the blood draws should occur last. The timing of the first 2 assessments should be such that it allows the blood draw (e.g., pharmacokinetics blood sample) to occur at the proper nominal time.

4.2.1 Enrollment/Screening Period

Table 5 shows all procedures to be conducted at the screening visit.

Table 5 Screening Schedule of Procedures

Study Period	Screening	
Visit Number	**V1**	**V2[f]**
Procedure/Study Day	**Day -28 to -11**	**Day -10 ± 3 days**
Written informed consent/assignment of E-code number	x	
Informed consent for future genetic research samples (optional)	x	
Informed consent for future non-genetic research samples (optional)	x	
Verify eligibility criteria	x	x
CLDQ-NASH and SF-36	x	
Dispensation/completion of diary (food intake)	x	x
Medical history, including smoking and alcohol history	x	
Demographics	x	
Physical examination (full)[a]	x	
Weight[b], height and BMI calculation	x	
dECG[c]	x	
Vital signs[d] (BP, pulse, body temperature, RR)	x	
ABPM[e]		x
MRI (including MRI-PDFF)[f]		x
Fibroscan[f]		x
AUDIT questionnaire	x	
Assessment of SAEs	x	x
Concomitant medications	x	x
SC injection training/demonstration/verify subject's ability to self-inject[g]	x	
Collect blood for:		
Serum chemistry	x	
Hematology	x	
Coagulation parameters	x	
Circulating markers (ALT, AST, GGT)	x	
Calcitonin	x	
HbA1c	x	
Lipase and amylase	x	
TSH	x	
Serum triglycerides	x	

Table 5 Screening Schedule of Procedures

Study Period	Screening	
Visit Number	**V1**	**V2[f]**
Procedure/Study Day	**Day -28 to -11**	**Day -10 ± 3 days**
Virology: hepatitis B surface antigen, hepatitis C virus antibody; HIV-1 and HIV-2	x	
FSH (postmenopausal females only)[h]	x	
ADA blood sample	x	
Collect urine for:		
Urinalysis	x	
Pregnancy test	x	
Drug and alcohol screen[i]	x	

ABPM = ambulatory blood pressure monitoring; ADA = anti-drug antibody; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUDIT = Alcohol Use Disorder Identification Test; BMI = body mass index; BP = blood pressure; CLDQ-NASH = Chronic Liver Disease Questionnaire for non-alcoholic steatohepatitis; dECG = digital electrocardiogram; eCRF = electronic case report form; FSH = follicle-stimulating hormone; GGT = gamma glutamyl transferase; HbA1c = hemoglobin A1c; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; MRI-PDFF = magnetic resonance imaging-proton density fat fraction; RR = respiratory rate; SAE = serious adverse event; SC = subcutaneous; SF-36 = Short-Form-36; E-code = subject identification number; TSH = thyroid stimulating hormone; V = visit.

[a] Only the screening physical examination will be a full examination. For all time points thereafter, only an abbreviated physical examination is required.

[b] Body weight should be measured in the morning, after the subject has toileted and removed bulky clothing, including shoes. Calibrated scales should be used.

[c] A single dECG recording should be performed after the subject has rested in the supine position for at least 10 minutes.

[d] Vital sign measurements should be measured after the subject has rested in the seated position for at least 10 minutes (rest period for dECG will suffice). Two consecutive BP readings should be taken at intervals of at least 1 minute, and the average recorded in the eCRF.

[e] Subjects will be fitted with the ABPM device while at the clinical unit, which may involve practice inflations. The subject will then wear the monitor/cuff for approximately 24 hours (including overnight at home) and will remove the device at home at the end of the 24-hour period.

[f] Subjects are required to fast for at least 8 hours overnight prior to Visit 2; subjects are permitted to drink water during this period of fasting. MRI-PDFF and fibroscan should be performed with the subject in a fasted state. Subjects with MRI (including MRI-PDFF) and fibroscan assessments performed within 60 days prior to screening do not need to undergo these assessments. If the screening MRI is determined to be of inadequate image quality by the MRI analysis vendor the subject may return for repeat MRI within the screening visit period.

[g] Subject's ability to administer a SC injection should be verified by undergoing a single SC injection using normal saline provided by the site. Willingness to perform this for the duration of the study should be discussed with the subject.

[h] FSH should only be checked in female subjects who are post-menopausal and have no previous confirmatory laboratory FSH result available.

[i] An alcohol breath test is an acceptable alternative to an alcohol urine test. If multiple tests are performed and conflicting results occur any positive result should be documented.

4.2.2 Randomized Treatment Period

Table 6 and Table 7 show all procedures to be conducted during the treatment period for MEDI0382/matched placebo 300 µg and MEDI0382/matched placebo 600 µg, respectively.

During the Coronavirus Disease 19 (COVID-19) Pandemic;

- If a subject is unable to attend clinic visits, and/or receive study intervention due to COVID-19, the site staff should keep in close contact with the subject, preferably through telephone calls at the time of the scheduled visit, to maintain awareness of their status. Assessments that can be performed over the phone should be completed such as adverse events, study drug administration and/or concomitant medications and any additional safety information and recorded in the eCRF and any assessments not performed should be recorded as 'not done'.
- If a subject is not able to attend their scheduled D78 MRI due to COVID-19 the MRI should be performed at the earliest opportunity and within 7 days of the original D78 scheduled date. All other subsequent visits should follow the original schedule.
- If a subject cannot attend their scheduled D133 visit due to COVID-19, every effort should be made to perform the visit within 2 days of the original D133 scheduled date, with the exception of the MRI which can be performed within 7 days of the original D133 scheduled date. If it is not possible to perform the visit within a 2-day window, then all assessments, excluding pharmacokinetic blood, should be performed at the earliest opportunity and within 7 days of the original D133 scheduled date where local regulations/public health guidance permit.

Table 6 MEDI0382/Matched Placebo 300 µg Treatment Period Schedule of Procedures

Study Period	**Treatment Period**											
	5-week Up-titration				**14-week Maintenance**							
Dose	**50 µg**		**100 µg**	**200 µg**	**300 µg**							
Visit Number	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Study Week	**1**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**19**
Procedure/Study Day	**D1**	**D2, 3, 4, 5, 6, 7**	**D8**	**D22**	**D36**	**D50 (± 2 days)**	**D64 (± 2 days)**	**D78 (± 2 days)**	**D92 (± 2 days)**	**D106 (± 2 days)**	**D120 (± 2 days)**	**D133**
Outpatient visit[a]	x	x	x	x	x	x	x	x	x	x	x	x
Daily visits for dosing[b]		x										
Dispense glucose meter[c]	x											
Verify eligibility criteria[d]	x											
Verify subject's ability to self-inject	x		x									
Verify subject fasted for 8 hours prior to visit	x							x				x
Randomization	x											
Dose initiation or up-titration	x		x	x	x							
Physical examination (abbreviated)	x		x	x	x	x	x	x	x	x	x	x
Weight[e] and BMI calculation	x		x	x	x	x	x	x	x	x	x	x
Height	x											
Waist and hip circumference	x							x				x
dECG[f]	x		x	x	x				x	x	x	x
Vital signs[g] (BP, pulse, body temperature, RR)	x		x	x	x				x	x	x	x
MRI (including MRI-PDFF)[h]	x							x				x
Fibroscan[h]	x							x				x
Assessments of AEs/SAEs	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x
Completion of diary (food intake / dosing)	→											

Table 6 MEDI0382/Matched Placebo 300 µg Treatment Period Schedule of Procedures

Study Period	**Treatment Period**											
	5-week Up-titration				**14-week Maintenance**							
Dose	**50 µg**		**100 µg**	**200 µg**	**300 µg**							
Visit Number	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Study Week	**1**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**19**
Procedure/Study Day	**D1**	**D2, 3, 4, 5, 6, 7**	**D8**	**D22**	**D36**	**D50 (± 2 days)**	**D64 (± 2 days)**	**D78 (± 2 days)**	**D92 (± 2 days)**	**D106 (± 2 days)**	**D120 (± 2 days)**	**D133**
IP dispensation for at home self-injection			x	x	x	x	x	x	x	x	x	
IP accountability				x	x	x	x	x	x	x	x	x
Collect blood[i] for:												
Serum chemistry	x				x			x				x
Hematology	x				x			x				x
Coagulation parameters	x											x
MEDI0382 pharmacokinetics[j]	x		x	x	x	x	x	x		x		x
ADA[k]	x		x		x			x		x		x
Circulating markers (ALT, AST, GGT)	x				x	x	x	x	x	x	x	x
TSH	x											x
Lipase and amylase	x											x
HbA1c	x							x				x
Calcitonin	x											x
Fasting lipid profile[l]	x							x				x
Free fatty acids, β-HB, aceto-acetate	x							x				x
Plasma glucose, insulin, glucagon, C-peptide and GLP-1	x							x				x

Table 6 MEDI0382/Matched Placebo 300 µg Treatment Period Schedule of Procedures

Study Period	**Treatment Period**											
	5-week Up-titration				**14-week Maintenance**							
Dose	**50 µg**		**100 µg**	**200 µg**	**300 µg**							
Visit Number	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Study Week	**1**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**19**
Procedure/Study Day	**D1**	**D2, 3, 4, 5, 6, 7**	**D8**	**D22**	**D36**	**D50 (± 2 days)**	**D64 (± 2 days)**	**D78 (± 2 days)**	**D92 (± 2 days)**	**D106 (± 2 days)**	**D120 (± 2 days)**	**D133**
Serum markers of liver fibrosis[m]	x							x				x
NIS4	x							x				x
Amino acids panel	x[n]							x				x
Adiponectin	x							x				x
Lipidomics	x							x				x
CK18 and ELF™	x							x				x
HOMA-IR calculation	x							x				x
Sample for future genetic testing (optional)	x											
Sample for future non-genetic testing (optional)	x							x				x
Collect urine for:												
Urinalysis	x				x			x				x
Pregnancy test (females of childbearing potential only)	x				x			x		x		x

Table 6 MEDI0382/Matched Placebo 300 µg Treatment Period Schedule of Procedures

Study Period	Treatment Period											
	5-week Up-titration				14-week Maintenance							
Dose	50 µg		100 µg	200 µg	300 µg							
Visit Number	3	4	5	6	7	8	9	10	11	12	13	14
Study Week	1	1	2	4	6	8	10	12	14	16	18	19
Procedure/Study Day	D1	D2, 3, 4, 5, 6, 7	D8	D22	D36	D50 (± 2 days)	D64 (± 2 days)	D78 (± 2 days)	D92 (± 2 days)	D106 (± 2 days)	D120 (± 2 days)	D133

ADA = anti-drug antibody; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-HB = β-hydroxybutyrate; BMI = body mass index; BP = blood pressure; C3M = neoepitope of metallopeptidase 9-mediated degraded type III collagen; C6M = neoepitope of matrix metallopeptidase 2-mediated degraded type VI collage; CK18 = cytokeratin 18; D = day; dECG = digital electrocardiogram; eCRF =electronic case report form; ELF™ = enhanced liver fibrosis score; GGT = gamma glutamyl transferase; GLP-1 = glucagon-like peptide-1; HbA1c = hemoglobin A1c; HDLc = high density lipoprotein cholesterol; HOMA-IR = Homeostatic model assessment of insulin resistance; IP = investigational product; LDLc = low density lipoprotein cholesterol; MRI-PDFF = magnetic resonance imaging-proton density fat fraction; NIS4 = non-invasive diagnostic score 4; P4NP7S = internal epitope in the 7S domain of type IV collagen; Pro-C3 = released N-terminal propeptide of type III collagen; Pro-C5 = released C-terminal propeptide of type V collagen; Pro-C6 = neoepitope in C-terminal of type VI collagen; RR = respiratory rate; T2DM = type 2 diabetes mellitus; TSH = thyroid stimulating hormone; SAE = serious adverse event

Unless stated otherwise, blood samples are to be taken in a fasted state.

Whenever vital signs, dECGs, and blood draws are scheduled for the same nominal time, the blood draws should occur last.

[a] Subjects are required to be dosed at the clinic for the 50 µg dose and on all study day visits when predose procedures are required. Subjects are required to fast for at least 8 hours overnight prior to Visits 3 (Day 1), 10 (Day 78) and 14 (Day 133); subjects are permitted to drink water during this period of fasting. On days where subjects attend the clinic in a fasted state, blood and urine samples should be obtained prior to administration of IP.

[b] Subjects are required to receive their doses at the clinic on Days 1-7, as preparation of the MEDI0382/matched placebo 50 µg dose necessitates dilution that must be performed by site staff. Subjects may travel to the site for daily visits during this time or alternatively should be given the option to stay overnight locally if this is more convenient.

[c] A glucose meter and test strips should be provided to subjects with T2DM. The subjects should be trained in their use and advised to test their capillary blood glucose level as per their usual schedule and if they have symptoms of hypoglycemia (hunger, dizziness, shaking, sweating, etc) or feel unwell.

[d] Check screening laboratory results and inclusion/exclusion criteria.

[e] Body weight should be measured predose in the morning while the subject is fasted (where applicable) and prior to breakfast, after the subject has toileted and removed bulky clothing, including shoes. Calibrated scales should be used.

[f] Triplicate dECG recording should be collected predose (within 20 minutes) on Visits 3 (Day 1), 5 (Day 8), 6 (Day 22), 7 (Day 36), and 14 (Day 133). At other time points, a single dECG recording will be collected predose (within 20 minutes). dECGs may be repeated per site's local procedure. The dECG triplicate recording should be taken prior to the pharmacokinetic samples for MEDI0382.

Table 6 MEDI0382/Matched Placebo 300 µg Treatment Period Schedule of Procedures

Study Period	Treatment Period											
	5-week Up-titration				14-week Maintenance							
Dose	50 µg		100 µg	200 µg	300 µg							
Visit Number	3	4	5	6	7	8	9	10	11	12	13	14
Study Week	1	1	2	4	6	8	10	12	14	16	18	19
Procedure/Study Day	D1	D2, 3, 4, 5, 6, 7	D8	D22	D36	D50 (± 2 days)	D64 (± 2 days)	D78 (± 2 days)	D92 (± 2 days)	D106 (± 2 days)	D120 (± 2 days)	D133

[g] Vital signs schedule:

- Visits 3 (Day 1), 5 (Day 8), 6 (Day 22), 7 (Day 36), and 14 (Day 133): predose (within 20 minutes) then 15, 30 and 60 minutes (± 5 minutes) and 2 hours (± 10 minutes).
- All other visits: predose (within 20 minutes).

For the predose BP measurements, two consecutive BP readings should be taken at intervals of at least 1 minute, and the average recorded in the eCRF.

[h] MRI (including MRI-PDFF) and fibroscan should be performed predose, in the morning with the subjects in a fasted state. The timing of the MRI and fibroscan should be kept as consistent as possible at each study visit where these assessments are required.

[i] Blood collection to be drawn predose if assessment occurs on a dosing day. Subjects should be in a fasted stated for blood collection drawn on Visits 3 (Day 1), 10 (Day 78) and 14 (Day 133). For other visits, subject should also be in fasted state for blood collection, whenever possible.

[j] MEDI0382 pharmacokinetic sampling schedule:

- For Visit 3 (Day 1), Visit 5 (Day 8), Visit 6 (Day 22), Visit 7 (Day 36): predose and 6 hours (± 30 minutes) postdose
- For Visit 8 (Day 50), Visit 9 (Day 64), Visit 10 (Day 78) and Visit 12 (Day 106): predose
- For Visit 14 (Day 133): predose and at 2, 4, 6, 8, 10, 24, 48, 96 hours (± 30 minutes) postdose. Subjects will be given the option to stay at the clinical study site or stay overnight locally, if this is more convenient.

[k] ADA samples will be collected prior to administration of MEDI0382.

[l] Lipid profile includes total cholesterol, LDLc, HDLc, and triglycerides.

[m] Markers of liver fibrosis (for collagen turnover) include Pro-C3, Pro-C5, Pro-C6, C3M, C6M and P4NP7S.

[n] Predose on Day 1.

Table 7 MEDI0382/Matched Placebo 600 µg Treatment Period Schedule of Procedures

Study Period	**Treatment Period**																		
	11-week Up-titration											**8-week Maintenance**							
Dose	**50 µg**		**100 µg**	**200 µg**	**300 µg**	**400 µg**			**500 µg**			**600 µg**							
Visit Number	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	
Study Week	**1**	**1**	**2**	**4**	**6**	**8**			**10**			**12**			**14**	**16**	**18**	**19**	
Procedure/Study Day	**D1**	**D2, 3, 4, 5, 6, 7**	**D8**	**D22**	**D36**	**D50**	**D51**	**D52**	**D64**	**D65**	**D66**	**D78**	**D79**	**D80**	**D92 (± 2 days)**	**D106 (± 2 days)**	**D120 (± 2 days)**	**D133**	
Outpatient visit[a]	x	x	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Daily visits for dosing[b]		x																	
Dispense glucose meter[c]	x																		
Verify eligibility criteria[d]	x																		
Verify subject's ability to self-inject	x		X																
Verify subject fasted for 8 hours prior to visit	x											x						x	
Randomization	x																		
Dose initiation or up-titration	x		X	x	x	x			x			x							
Physical examination (abbreviated)	x		X	x	x	x			x			x			x	x	x	x	
Weight[e] and BMI calculation	x		X	x	x	x			x			x			x	x	x	x	
Height	x																		
Waist and hip circumference	x											x						x	

Table 7 MEDI0382/Matched Placebo 600 µg Treatment Period Schedule of Procedures

Study Period	**Treatment Period**																	
	11-week Up-titration											**8-week Maintenance**						
Dose	**50 µg**		**100 µg**	**200 µg**	**300 µg**	**400 µg**			**500 µg**			**600 µg**						
Visit Number	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Study Week	**1**	**1**	**2**	**4**	**6**	**8**			**10**			**12**			**14**	**16**	**18**	**19**
Procedure/Study Day	**D1**	**D2, 3, 4, 5, 6, 7**	**D8**	**D22**	**D36**	**D50**	**D51**	**D52**	**D64**	**D65**	**D66**	**D78**	**D79**	**D80**	**D92 (± 2 days)**	**D106 (± 2 days)**	**D120 (± 2 days)**	**D133**
dECG[f]	x		X	x	x	x			x			x			x	x	x	x
Vital signs[g] (BP, pulse, body temperature, RR)	x		X	x	x	x	x[h]	x[h]	x	x[h]	x[h]	x	x[h]	x[h]	x	x	x	x
ABPM[i]						x			x			x						x
MRI-PDFF[j]	x											x						x
Fibroscan[j]	x											x						x
Assessments of AEs/SAEs	x	x	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications	x	x	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Completion of diary (food intake / dosing)	→																	
IP dispensation for at home self-injection			X	x	x	x			x			x			x	x	x	
IP accountability				x	x	x			x			x			x	x	x	x
Collect blood[k] for:																		
Serum chemistry	x				x	x	x	x	x	x	x	x	x	x				x
Hematology	x				x							x						x
Coagulation parameters	x																	x

Table 7 MEDI0382/Matched Placebo 600 µg Treatment Period Schedule of Procedures

Study Period	**Treatment Period**																	
	11-week Up-titration											**8-week Maintenance**						
Dose	**50 µg**		**100 µg**	**200 µg**	**300 µg**	**400 µg**			**500 µg**			**600 µg**						
Visit Number	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Study Week	**1**	**1**	**2**	**4**	**6**	**8**			**10**			**12**			**14**	**16**	**18**	**19**
Procedure/Study Day	**D1**	**D2, 3, 4, 5, 6, 7**	**D8**	**D22**	**D36**	**D50**	**D51**	**D52**	**D64**	**D65**	**D66**	**D78**	**D79**	**D80**	**D92 (± 2 days)**	**D106 (± 2 days)**	**D120 (± 2 days)**	**D133**
MEDI0382 pharmacokinetics[l]	x		X	x	x	x			x			x				x		x
ADA[m]	x		X		x							x				x		x
Circulating markers (ALT, AST, GGT)	x				x	x			x			x			x	x	x	x
TSH	x																	x
Lipase and amylase	x																	x
HbA1c	x											x						x
Calcitonin	x																	x
Fasting lipid profile[n]	x											x						x
Free fatty acids, β-HB, aceto-acetate	x											x						x
Plasma glucose, insulin, glucagon, c-peptide, and GLP-1	x					x	x	x	x	x	x	x	x	x				x
Serum markers of liver fibrosis[o]	x											x						x

Table 7 MEDI0382/Matched Placebo 600 µg Treatment Period Schedule of Procedures

Study Period	**Treatment Period**																		
	11-week Up-titration											**8-week Maintenance**						
Dose	**50 µg**		**100 µg**	**200 µg**	**300 µg**	**400 µg**			**500 µg**			**600 µg**						
Visit Number	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Study Week	**1**	**1**	**2**	**4**	**6**	**8**			**10**			**12**			**14**	**16**	**18**	**19**
Procedure/Study Day	**D1**	**D2, 3, 4, 5, 6, 7**	**D8**	**D22**	**D36**	**D50**	**D51**	**D52**	**D64**	**D65**	**D66**	**D78**	**D79**	**D80**	**D92 (± 2 days)**	**D106 (± 2 days)**	**D120 (± 2 days)**	**D133**
NIS4	x											x						x
Amino acids panel	x[p]											x						x
Adiponectin	x											x						x
Lipidomics	x											x						x
CK18 and ELF™	x											x						x
HOMA-IR calculation	x											x						x
Sample for future genetic testing (optional)	x																	
Sample for future non-genetic testing (optional)	x											x						x
Collect urine for:																		
Urinalysis	x				x							x						x
Pregnancy test (females of childbearing potential only)	x				x							x				x		x

Table 7 MEDI0382/Matched Placebo 600 µg Treatment Period Schedule of Procedures

Study Period	Treatment Period																		
	11-week Up-titration											8-week Maintenance							
Dose	50 µg		100 µg	200 µg	300 µg	400 µg			500 µg			600 µg							
Visit Number	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
Study Week	1	1	2	4	6	8			10			12			14	16	18	19	
Procedure/Study Day	D1	D2, 3, 4, 5, 6, 7	D8	D22	D36	D50	D51	D52	D64	D65	D66	D78	D79	D80	D92 (± 2 days)	D106 (± 2 days)	D120 (± 2 days)	D133	

ABPM = ambulatory blood pressure monitoring; ADA = anti-drug antibody; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-HB = β-hydroxybutyrate; BMI = body mass index; BP = blood pressure; C3M = neoepitope of metallopeptidase 9-mediated degraded type III collagen; C6M = neoepitope of matrix metallopeptidase 2-mediated degraded type VI collage; CK18 = cytokeratin 18; D = day; dECG = digital electrocardiogram; eCRF = electronic case report form; GGT = gamma glutamyl transferase; GLP-1 = glucagon-like peptide-1; ELF™ = enhanced liver fibrosis score; HbA1c = hemoglobin A1c; HDLc = high density lipoprotein cholesterol; HOMA-IR = Homeostatic model assessment of insulin resistance; IP = investigational product; LDLc = low density lipoprotein cholesterol; MRI-PDFF = magnetic resonance imaging-proton density fat fraction; NIS4 = non-invasive diagnostic score 4; P4NP7S = internal epitope in the 7S domain of type IV collagen; Pro-C3 = released N-terminal propeptide of type III collagen; Pro-C5 = released C-terminal propeptide of type V collagen; Pro-C6 = neoepitope in C-terminal of type VI collagen; RR = respiratory rate; T2DM = type 2 diabetes mellitus; TSH = thyroid stimulating hormone; SAE = serious adverse event

Unless stated otherwise, blood samples are to be taken in a fasted state.

Whenever vital signs, dECGs, and blood draws are scheduled for the same nominal time, the blood draws should occur last.

[a] Subjects are required to be dosed at the clinic for the 50 µg dose and on study day visits when predose procedures are required. Subjects are required to fast for at least 8 hours overnight prior to Visits 3 (Day 1), 14 (Day 78) and 20 (Day 133); subjects are permitted to drink water during this period of fasting. On days where subjects attend the clinic in a fasted state, blood and urine samples should be obtained prior to administration of IP. Subjects are required to visit the clinic on two subsequent days following up-titration to the 400, 500 and 600 µg dose for safety monitoring; subjects may travel to the site for daily visits during this time or alternatively should be given the option to stay overnight locally if this is more convenient.

[b] Subjects are required to receive their doses at the clinic on Days 1-7, as preparation of the MEDI0382/matched placebo 50-µg dose necessitates dilution that must be performed by site staff. Subjects may travel to the site for daily visits during this time or alternatively should be given the option to stay overnight locally if this is more convenient.

[c] A glucose meter and test strips should be provided to subjects with T2DM. The subjects should be trained in its use and advised to test their capillary blood glucose level as per their usual schedule and if they have symptoms of hypoglycemia (hunger, dizziness, shaking, sweating, etc) or feel unwell.

[d] Check screening labs and inclusion/exclusion criteria.

[e] Body weight should be measured predose in the morning while the subject is fasted (where applicable) and prior to breakfast, after the subject has toileted and removed bulky clothing, including shoes. Calibrated scales should be used.

Table 7 MEDI0382/Matched Placebo 600 µg Treatment Period Schedule of Procedures

Study Period	Treatment Period																		
	11-week Up-titration											8-week Maintenance							
Dose	50 µg		100 µg	200 µg	300 µg	400 µg			500 µg			600 µg							
Visit Number	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	
Study Week	1	1	2	4	6	8			10			12			14	16	18	19	
Procedure/Study Day	D1	D2, 3, 4, 5, 6, 7	D8	D22	D36	D50	D51	D52	D64	D65	D66	D78	D79	D80	D92 (± 2 days)	D106 (± 2 days)	D120 (± 2 days)	D133	

[f] Triplicate dECG recording should be collected predose (within 20 minutes) on Visits 3 (Day 1), 5 (Day 8), 6 (Day 22), 7 (Day 36), 8 (Day 50), 11 (Day 64), 14 (Day 78), and 20 (Day 133). At other time points, a single dECG recording will be collected predose (within 20 minutes). dECGs may be repeated per site's local procedure. The dECG triplicate recording should be taken prior to the pharmacokinetic samples of MEDI0382.

[g] Vital signs schedule:

- Visits 3 (Day 1), 5 (Day 8), 6 (Day 22), 7 (Day 36), 8 (Day 50), 11 (Day 64), 14 (Day 78), and 20 (Day 133): predose (within 20 minutes) then 15, 30 and 60 minutes (± 5 minutes) and 2 hours (± 10 minutes).
- All other visits: predose (within 20 minutes).

For the predose BP measurement, two consecutive BP readings should be taken at intervals of at least 1 minute, and the average recorded in the eCRF. On days when ABPM is due to be checked, a set of vital signs should be performed prior to application of the ABPM cuff.

[h] Orthostatic BP is to be taken predose at the timepoints specified above. Measurement of orthostatic BP changes will be performed as follows:

- After the subject has been supine for a minimum of 5 minutes, BP and pulse rate will be measured in duplicate (at least 1 minute apart).
- Immediately after supine measurements, a standing BP and pulse rate will be measured in duplicate as follows:
- First measurement: BP and pulse rate measured after at least 1 minute of standing.
- Second measurement: BP and pulse rate measured after at least 3 minutes of standing.

Orthostatic hypotension is defined as a drop of 20 mmHg in systolic BP or a drop of 10 mmHg in diastolic BP within 2 to 5 minutes of standing up, or if standing causes signs and symptoms.

[i] Subjects will be fitted with the ABPM device while at the clinical unit, which may involve practice inflations. The subject will wear the monitor/cuff for approximately 24 hours (including overnight at home) and will remove the device at home at the end of the 24-hour period and return the monitor at their next visit.

[j] MRI (including MRI-PDFF) and fibroscan should be performed predose in the morning with the subjects in a fasted state. The timing of the MRI (including MRI-PDFF) and fibroscan should be kept as consistent as possible at each study visit where these assessments are required.

[k] Blood collection to be drawn predose if assessment occurs on a dosing day. Subjects should be in a fasted state for blood collection drawn on Visits 3 (Day 1), 14 (Day 78) and 20 (Day 133). For other visits, subject should also be in fasted state for blood collection, whenever possible.

[l] MEDI0382 pharmacokinetic sampling schedule:

Table 7 MEDI0382/Matched Placebo 600 µg Treatment Period Schedule of Procedures

Study Period	Treatment Period																	
	11-week Up-titration											8-week Maintenance						
Dose	50 µg		100 µg	200 µg	300 µg	400 µg			500 µg			600 µg						
Visit Number	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Study Week	1	1	2	4	6	8			10			12			14	16	18	19
Procedure/Study Day	D1	D2, 3, 4, 5, 6, 7	D8	D22	D36	D50	D51	D52	D64	D65	D66	D78	D79	D80	D92 (± 2 days)	D106 (± 2 days)	D120 (± 2 days)	D133

- ! For Visit 3 (Day 1), Visit 5 (Day 8), Visit 6 (Day 22), Visit 7 (Day 36), Visit 8 (Day 50), Visit 11 (Day 64), and Visit 14 (Day 78): predose and 6 hours (± 30 minutes) postdose
- ! For Visit 18 (Day 106) predose
- ! For Visit 20 (Day 133): predose and at 2, 4, 6, 8, 10, 24, 48, 96 hours (± 30 minutes) postdose. Subjects will be given the option to stay at the clinical study site or stay overnight locally, if this is more convenient.

[m] ADA samples will be collected prior to administration of MEDI0382.
[n] Lipid profile includes total cholesterol, LDLc, HDLc, and triglycerides.
o Markers of liver fibrosis (for collagen turnover) include Pro-C3, Pro-C5, Pro-C6, C3M, C6M, and P4NP7S.
[p] Predose on Day 1.

4.2.3 Follow-up Period

Table 8 shows all procedures to be conducted during the follow-up period.

Table 8 Schedule of Follow-up Procedures

Study Period	Follow-up Period/Early Discontinuation[e]
Visit Number	**Visit 15/21 (EoS)**
Study Week	**23**
Procedure/Study Day	**D161 (± 3 days)**
Physical examination (abbreviated)	x
Weight and BMI calculation	x
dECG	x
Vital signs[a] (BP, pulse, body temperature, RR)	x
Assessment of AEs/SAEs	x
Concomitant medications	x
Completion (food intake) / collection of diary	x
Collect blood for:	
Serum chemistry	x
Hematology	x
Coagulation parameters	x
HbA1c	x
ADA[b]	x
Circulating markers (ALT, AST, GGT)	x
Calcitonin[c]	x
Lipid profile[d], free fatty acids, β-HB, aceto-acetate	x
Collect urine for:	
Urinalysis	x
Pregnancy test (females of childbearing potential only)	x
For Early discontinuation visit, the following should be performed in addition to the above[e]:	
IP accountability	x
MRI-PDFF[f]	x
Fibroscan	x
MEDI0382 pharmacokinetics[g]	x

Table 8 Schedule of Follow-up Procedures

Study Period	Follow-up Period/Early Discontinuation[e]
Visit Number	Visit 15/21 (EoS)
Study Week	23
Procedure/Study Day	D161 (± 3 days)

ADA = anti-drug antibody; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-HB = β-hydroxybutyrate; BMI = body mass index; BP = blood pressure; D = day; dECG = digital electrocardiogram; EoS = end of study; GGT = gamma glutamyl transferase; HbA1c = hemoglobin A1c; HDLc = high-density lipoprotein cholesterol; LDLc = low-density lipoprotein cholesterol; MRI-PDFF = magnetic resonance imaging-proton density fat fraction; RR = respiratory rate; SAE = serious adverse event; ULN = upper limit of normal.

[a] For BP measurements, two consecutive readings should be taken at intervals of at least 1 minute, and the average recorded in the eCRF.

[b] If this sample is ADA positive, the subject will be asked to return to provide another sample at approximately 3 months after the end of study visit. If that sample is ADA positive, additional visit(s) approximately every 3 months should continue until a sample tests negative for ADA or return to baseline level.

[c] Calcitonin need only be re-measured in subjects who had a level > ULN on Day 133.

[d] Lipid profile include total cholesterol, LDLc, HDLc, and triglycerides.

[e] Subjects are required to fast for at least 8 hours prior to the Early Discontinuation Visit; subjects are permitted to drink water during this period of fasting. Subjects should be asked to return within 7 days from last investigational product dose, where possible. Subjects should also be asked to return 28 days (±3 days) from the last investigational product dose for follow-up assessments unless they are unable or unwilling to return.Subjects who discontinue investigational product but wish to continue with study assessments should first perform the Early Discontinuation Visit and then continue the assessments as described in Table 6 or Table 7 as appropriate. Subjects who discontinue from investigational product but continue on the study should not have more than 3 MRIs performed within the study treatment period (following randomization).

[f] MRI (including MRI-PDFF) and fibroscan should be performed predose in the morning with the subjects in a fasted state. Subjects who discontinue from investigational product but continue on the study should not have more than 3 MRIs performed within the study treatment period (following randomization).

[g] One pharmacokinetic sample should be taken at any time during the visit, but should be as close to the ADA sample as possible.

4.3 Description of Study Procedures

4.3.1 Efficacy

Changes in HFF will be assessed by MRI-PDFF (Section 4.3.5.1).

4.3.2 Safety

4.3.2.1 Medical History

Complete medical history will include history and current medical conditions, past or present cardiovascular disorders, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, dermatological, psychiatric, genitourinary, drug and surgical history, or any other diseases or disorders.

Smoking and alcohol history will also be recorded.

In addition, the subjects will be asked the following questions:

- In the last 2 years, have you ever been treated with high dose Vitamin E to manage NASH (or any other condition)?
- Did your prescriber consider your response adequate or inadequate?
- In the last 2 years, have you ever been treated with pioglitazone to manage NASH (or any other condition)?
- Did your prescriber consider your response adequate or inadequate?
- When was the last time you tried weight loss and exercise?
- Did you lose weight that time and have you been successful keeping the new weight?

The AUDIT questionnaire (Appendix F and Appendix G) to assess alcohol use habits will be completed at screening only (Table 5). The results will be used for determining subject eligibility (Section 4.1.3).

4.3.2.2 Physical Examination

The full physical examination includes an assessment of the following: general appearance including skin inspection, lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular system, lungs, abdomen, and reflexes.

The abbreviated physical examination includes the following: skin, extremities, cardiovascular system, lungs, and abdomen.

Physical examinations will be performed at the time points specified in the schedule of procedures (Table 5, Table 6, Table 7, and Table 8). Investigators should pay special attention to clinical signs related to previous serious illnesses; new or worsening abnormalities may qualify as AEs (additional details are provided in Section 5). In addition, the injection site will be assessed.

At study termination clinically significant abnormalities in physical examination findings at study termination must be followed up by the investigator and evaluated with additional tests if necessary, until the underlying cause is diagnosed, or resolution occurs.

4.3.2.3 Digital Electrocardiogram

Digital ECGs will be recorded at the sites according to Table 5, Table 6, Table 7, and Table 8. Subjects should rest in the supine position at least 10 minutes before dECG recordings are conducted. Digital ECGs may be repeated per site's local procedure. The dECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the clinical study site. The investigator should date and sign the dECG tracing and record the clinical

significance of any abnormal result on the tracing. Digital ECG evaluation will be recorded in the eCRF.

Paper copies of the dECGs will be stored at the study site and digital copies transmitted to a central archive. Digital copies may be interpreted where required by other qualified physicians outside the study site.

The following variables will be reported: PR, QRS, QT, HR, QTcB and QTcF intervals. The investigator may add extra 12-lead dECG safety assessments if there are any abnormal findings or if the investigator considers it is required for any other safety reason.

4.3.2.4 Vital Signs

Vital sign measurements will be obtained at the visits specified in Table 5, Table 6, Table 7, and Table 8. Body temperature and respiratory rate will be measured after the subject has rested in the seated position for at least 10 minutes in a quiet setting without distractions. Postural BP changes should be measured as described below. Vital sign measurements should be taken prior to investigational product administration (where applicable) and before blood drawing. BP, and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Route of body temperature measurement will be according to local procedures but should be consistent throughout the study for an individual subject.

Orthostatic hypotension is defined as a drop of 20 mmHg in systolic BP or a drop of 10 mmHg in diastolic BP within 2 to 5 minutes of standing up, or if standing causes signs and symptoms.

Measurement of postural BP changes will be performed as follows:

- After the subject has been in the supine position for a minimum of 5 minutes, BP and pulse rate will be measured in duplicate (at least 1 minute apart).
- Standing BP and pulse rate will be measured in duplicate as follows:
  - First measurement: BP and pulse rate measured after at least 1 minute of standing.
  - Second measurement: BP and pulse rate measured after at least 3 minutes of standing.

On days where ambulatory blood pressure monitoring (ABPM) is due to be checked, a predose set of vital signs should be performed prior to application of the ABPM cuff. BP should be measured once with the arm at heart level with the subject supine for at least 10 minutes prior to the measurement and measurements performed using an adequate arm cuff size. For time points where dECG recording precedes vital sign measurement, the 10-minute

rest in the supine position prior to the dECG suffices for the rest prior to vital sign measurement. The pulse rate should be measured for 30 seconds to determine the rate.

Training for Application and Wearing of ABPM Device

Subjects will be given training at their local study site about how to set up and apply the ABPM device. In brief, an appropriate size BP cuff will be selected, and the device will be fitted to the nondominant arm of the subject, with the bladder placed over the artery and an initial test reading performed. The subjects will be advised that for the first reading, the device will inflate to a pressure of 180 mmHg, and thereafter the device will adapt to inflate to a pressure just above the last recorded BP. The subject will be advised to undergo normal daily activities while wearing the cuff, and he/she will be advised to avoid any strenuous form of activity, bathing or showering while wearing the cuff. The subject will be advised to remain still during a measurement with the arm relaxed at heart level. The subject will also be given advice on how to wear the device during the day and at night while sleeping, and what to expect in terms of frequency of readings during the day and overnight. During ABPM, systolic BP, diastolic BP, heart rate pressure, heart rate, and mean arterial pressure readings will be recorded over a period of 24 hours.

4.3.2.5 Weight, Height, BMI, Waist and Hip Circumference

Height and body weight will be measured at the time points specified in Table 5, Table 6, Table 7, and Table 8. Body mass index will be calculated directly in RAVE [BMI = weight/(height)^2], where weight is measured in kg, and height in meters). The height measurement recorded at screening will be used to calculate BMI for the eligibility assessment. The height measurement recorded at Visit 3 (Day 1) will be used for each subsequent BMI calculation.

Waist and hip circumference will be measured at the time points specified in the schedules of procedures (Table 5, Table 6, Table 7, and Table 8). The correct position for measuring waist circumference is midway between the uppermost border of the iliac crest and the lower border of the costal margin. A measuring tape of adequate length should be placed around the abdomen at the level of this midway point and a reading taken when the tape is snug but does not compress the skin, and at the end of a normal respiratory expiration. Hip circumference should be measured around the widest portion of the buttocks, with the tape parallel to the floor. Waist-hip ratio is calculated as waist measurement divided by hip measurement (ie, waist ÷ hip). For both measurements, the subject should stand with feet close together, arms at the side and body weight evenly distributed. Each measurement should be repeated twice; if the measurements are within 1 cm of one another, the average should be calculated. If the difference between the 2 measurements exceeds 1 cm, the 2 measurements should be repeated.

[redacted]

CCI [redacted]

4.3.5 Pharmacodynamic Evaluation and Methods

4.3.5.1 Magnetic Resonance Imaging (Including MRI-PDFF)

MRI (including MRI-PDFF) will be performed, at the time points specified in Table 5, Table 6, Table 7 and Table 8 according to the Imaging Manual to assess HFF, CCI [redacted]. Subjects with an MRI-PDFF assessment performed within 60 days prior to screening do not need to repeat this assessment at Visit 2 (Day -10). If the screening MRI is determined to be of inadequate image quality by the MRI analysis vendor the subject may return for repeat MRI within the screening visit period

4.3.5.2 Fibroscan

Fibroscan will be performed, at the time points specified in Table 5, Table 6, Table 7 and Table 8 to assess liver stiffness and attenuation parameters. Subjects with a fibroscan assessment performed within 60 days prior to screening do not need to repeat this assessment at Visit 2 (Day -10).

4.3.6 Clinical Laboratory Tests

A Laboratory Manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical research study.

Clinical laboratory safety tests will be performed in a central clinical laboratory. Urine pregnancy tests may be performed at the site using a licensed test (dipstick). Abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

All clinical laboratory tests will be performed according to the timing and frequency presented in Table 5, Table 6, Table 7, and Table 8. All protocol-required laboratory assessments must be conducted in accordance with the Laboratory Manual.

The investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at center as source data for laboratory variables. The investigator should follow all clinically significant laboratory abnormalities occurring during the study that were not present at baseline. These abnormalities should be evaluated with additional tests, if necessary, until the underlying cause is diagnosed, or resolution occurs. The diagnosis and resolution date must be reported to the sponsor.

Information about how AEs based on laboratory tests should be recorded and reported are provided in Section 5.

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

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

Serum chemistry

- blood urea nitrogen
- creatinine
- total protein
- albumin
- TBL
- alkaline phosphatase (ALP)
- ALT
- AST
- calcium
- glucose (fasting where required)
- sodium
- potassium
- chloride
- bicarbonate
- phosphorus
- gamma glutamyl transferase

Notes for serum chemistry

Tests for AST, ALT, ALP, and TBL must be conducted concurrently and assessed concurrently.

The additional collection time points for circulating markers (ALT, AST, GGT) should be noted (Table 5, Table 6, Table 7, and Table 8).

Hematology

- red blood cell count
- hemoglobin
- hematocrit
- absolute white blood cell count
- white blood cell count with percent differential
- platelet count
- mean cell volume
- mean corpuscular hemoglobin concentration
- mean corpuscular hemoglobin

Coagulation parameters

- prothrombin time
- activated partial thromboplastin time
- thrombin time
- international normalized ratio

Urinalysis

- pH
- specific gravity
- glucose
- blood (urine hemoglobin/erythrocytes/blood)
- ketones
- protein
- microscopic analysis (if positive for blood, nitrites, or protein)
- bilirubin

- color
- appearance
- nitrites
- leukocytes
- urobilinogen

Females only

- pregnancy test: urine human chorionic gonadotropin (hCG) (females of childbearing potential)
- follicle stimulating hormone (FSH) (post-menopausal women only)

Screening only

- human immunodeficiency virus (HIV)-1 and HIV-2 antibodies
- drug and alcohol screen
- hepatitis B surface antigen (HBsAg) and hepatitis C antibody (anti-HCV)

Additional laboratory assessments

- calcitonin
- HbA1c
- thyroid stimulation hormone (TSH)
- total cholesterol
- low-density lipoprotein cholesterol (LDLc)
- high-density lipoprotein cholesterol (HDLc),
- amino acid panel
- collagen turnover (markers of liver fibrosis)
- lipidomics
- enhanced liver fibrosis (ELF™)
- triglycerides
- amylase and lipase
- plasma glucose, insulin, glucagon, c-peptide, and GLP-1
- free fatty acids
- beta-hydroxybutyrate
- aceto-acetate
- non-invasive diagnostic score 4 (NIS4)
- adiponectin: total and high molecular weight
- CK18

4.3.7 Pharmacokinetic Evaluation and Methods

Blood will be collected at predose and at specific postdose times to evaluate pharmacokinetics of MEDI0382 in plasma at the time points specified in Table 5, Table 6, Table 7, and Table 8. The pharmacokinetics of MEDI0382 in plasma will be measured utilizing a validated liquid chromatography-tandem mass spectrometry method (LC-MS/MS).

4.3.8 Immunogenicity Evaluation and Methods

Immunogenicity blood samples will be collected to evaluate ADA responses to MEDI0382. Anti-drug antibody sampling will occur by groups(s) at the time points specified in Table 5, Table 6, Table 7, and Table 8. A validated screening assay will be used to determine ADA positive samples. Any positive samples will be tested in a confirmatory assay whereby the specificity of the ADA response will be confirmed as either positive or negative with respect to MEDI0382. Titer evaluation and cross-reactivity to GLP-1 and glucagon may be performed

on samples that are confirmed positive for ADA. Serum samples collected for ADA should be stored as described in the Laboratory Manual.

Additional immunogenicity data will be reported in the clinical study report (CSR) or in an addendum, if applicable. Additional analyses may be conducted on anonymized, individual or pooled immunogenicity samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR. Immunogenicity samples will be retained until point of license for this program and may be utilized for further characterization of the antibody response.

4.3.9 Genetic Evaluations and Method

The subject's consent to participate in the genetic research components of the study is optional. See Appendix E or further information.

4.3.10 Biomarker Evaluation

CCI [redacted]

4.3.11 Storage, Re-use and Destruction of Biological Samples

Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed.

4.3.12 Estimate of Volume of Blood to be Collected

The estimated volume of blood to be collected from each subject over the entire course of their participation in the study is approximately 461 mL, plus an optional 60 mL for the MEDI0382 300 µg/matched placebo group and 557 mL, plus an optional 60 mL for the MEDI0382 600 µg/matched placebo group.

4.4 Study or Study Component Suspension or Termination

MedImmune reserves the right to temporarily suspend or permanently terminate this study or component of the study at any time. The reasons for temporarily suspending or permanently terminating the study may include but are not limited to the following:

1 The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects

2 Subject enrollment is unsatisfactory
3 Non-compliance that might significantly jeopardize the validity or integrity of the study
4 Sponsor decision to terminate development of the investigational product for this indication
5 Sponsor decision to terminate the study based on a planned futility analysis

If MedImmune determines that temporary suspension or permanent termination of the study or component of the study is required, MedImmune will discuss the reasons for taking such action with all participating investigators (or head of the medical institution, where applicable). When feasible, MedImmune will provide advance notice to all participating investigators (or head of the medical institution, where applicable) of the impending action.

If the study or component of the study is suspended or terminated for safety reasons, MedImmune will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. MedImmune will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) promptly and provide the reason(s) for the suspension/termination. If the study or component of the study is suspended for safety reasons and it is deemed appropriate by MedImmune to resume the study or component of the study, approval from the relevant regulatory authorities (and IRBs/IECs when applicable) will be obtained prior to resuming the study.

4.5 Investigational Products

4.5.1 Identity of Investigational Product(s)

MedImmune will provide the investigator(s) with investigational product (Table 9) and diluent using designated distribution centers.

Table 9 Identification of Investigational Products

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
MEDI0382	MedImmune	2 mg/mL sterile liquid formulation, 1 mL nominal volume. Single dose vial.
Matched placebo	MedImmune	Sterile liquid formulation buffer, 1 mL nominal volume. Single dose vial

Note: Diluent solution (manufactured by sponsor) will be provided to sites.
Note that the diluent solution is the same as the placebo.

MEDI0382 is provided as a sterile liquid drug product (nominal concentration of 2 mg/mL) in 50 mM sodium phosphate buffer containing 1.85% weight per volume (w/v) propylene glycol, pH 7.8 intended for SC administration.

Matched placebo is provided as a sterile solution of 50 mM sodium phosphate buffer containing 1.85% (w/v) propylene glycol, pH 7.8 intended for SC administration.

Investigational product will be supplied to the site in blinded kits each containing 1 vial. Each kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label on the vial within the carton). When investigational product is dispensed for at-home dosing, the site should transfer the required number of 1 vial kits into the supplied empty, double-blind labelled carton, which can hold up to 8 single vial kits.

4.5.1.1 Investigational Product Handling

In-clinic Investigational Product Handling

Investigational product should be stored at 2°C to 8°C in the original container and should be protected from heat and light.

Investigational products are supplied in single-use vials and do not contain preservatives, so after dose preparation any unused portion must be discarded. Preparation of syringes for dose administration is to be performed using aseptic techniques. Total in-use storage time from needle puncture of the investigational product vial to start of administration should not exceed 4 hours at room temperature. If storage time exceeds these limits, a new dose must be prepared from a new vial.

At-home Investigational Product Handling

The entire carton of investigational product should be stored in the refrigerator. Subjects should be asked to ensure they have a normal domestic refrigerator at home, which should be between 2°C and 8°C. Investigational product should be protected from heat and light.

Subjects should be instructed not to store the investigational product directly adjacent to the refrigerator cooling element. Investigational product should not be used if it has been frozen.

The subject should be instructed to remove from the refrigerator only the 1-vial kit required for their daily dose. All other kits are to be kept in the original carton in the refrigerator until required.

4.5.1.2 Investigational Product Inspection

Each vial selected for dose preparation should be inspected prior to use. The MEDI0382 or placebo solution in vials should not be cloudy, discolored, or contain any visible particles. If there are any defects noted with the investigational product, the investigator and site monitor

should be notified immediately. Refer to the Product Complaint section (Section 4.5.1.6) for further instructions.

4.5.1.3 Dose Preparation Steps

No incompatibilities between MEDI0382 and plastics passing compatibility tests (ie, polyolefin or polyvinylchloride bags) have been observed.

In-clinic Dose Preparation

Investigational product is supplied in 3 mL glass vials at a nominal concentration of 2 mg/mL. The final delivery volume and concentration for each dose period and the syringe sizes to be used for preparation are described in Table 10. No incompatibilities have been observed between 2 mg/mL MEDI0382 stock solution and plastics passing compatibility tests (ie, polypropylene syringes). The diluted stock must be prepared and administered using 1 mL polypropylene syringes; the diluted stock is incompatible with 0.3 mL insulin syringes.

For the MEDI0382/matched placebo 50 µg dose, a 10-fold dilution of the supplied stock is required. Dilutions must be prepared by site staff at the clinical unit prior to administration in the clinic. Only the supplied diluent may be used for this dilution step.

If dilution is required, investigational product should be removed from the refrigerator and kept at room temperature for at least 30 minutes and a maximum of 4 hours for temperature equilibration. If no dilution is required, 15 minutes is recommended for temperature equilibration.

To make a 10-fold dilution of MEDI0382 or placebo, it is recommended to withdraw 0.1 mL of the supplied investigational product using a 1 mL syringe and 27 G needle and add it into a sterile empty vial. Using a new 1 mL syringe and 27 G needle, add 0.9 mL of diluent into the same vial. The vial should be mixed by swirling gently to make a homogenous final admixture. Do not shake. The diluted dose should be administered using a 1.0 mL syringe (Table 10). Dilution and preparation of doses for administration is to be performed using aseptic techniques.

Doses of 100 µg or greater do not require a dilution step and should be administered directly using a 0.3 mL insulin syringe.

Table 10 MEDI0382 and Placebo Dose Preparation

Dose Period	MEDI0382 Concentration (mg/mL)	Volume of Injection (mL)	Syringe Size to be Used for Dose Administration (mL)	Number of Units[a]
50 µg or placebo[b]	0.2	0.25	1.0	NA
100 µg or placebo	2.0	0.05	0.3	5
200 µg or placebo	2.0	0.10	0.3	10
300 µg or placebo	2.0	0.15	0.3	15
400 µg or placebo	2.0	0.20	0.3	20
500 µg or placebo	2.0	0.25	0.3	25
600 µg or placebo	2.0	0.30	0.3	30

NA = not applicable

[a] The 0.3 mL insulin syringe is marked in 'units' where each unit = 0.01 mL, and 0.3 mL = 30 units.

[b] For MEDI0382/matched placebo doses of 50 µg, a 10-fold diluted stock concentration of 0.2 mg/mL will be prepared by site staff at the clinical unit, prior to administration.

At-home Dose Preparation

Only doses of 100 µg or above can be administered at home. No dilution steps are required for these doses, and subjects should withdraw the required volume directly from the supplied vial using a 0.3 mL insulin syringe prior to administration.

Prior to administration at home, the single vial of investigational product to be used for injection should be removed from the refrigerator and kept at room temperature for approximately 15 minutes for temperature equilibration. The subject is not to administer investigational product if the time outside of the refrigerator exceeds 4 hours; if storage time exceeds this limit, a new dose must be prepared from a new vial.

4.5.1.4 Treatment Administration

In-clinic Treatment Administration

The first day of dosing is considered Day 1. On the day of each dose, investigational product will be administered according to the schedule of procedures, as soon as practical upon waking each morning prior to breakfast, ideally at the same time each day. Investigational product will be administered by the subject under supervision as an SC injection in the lower abdomen using either a 1 mL syringe for 50 µg doses, or a 0.3 mL insulin syringe for the 100 to 600 µg doses.

At-home Treatment Administration

A dose is to be self-administered by SC injection once daily using a 0.3 mL insulin syringe for 100 to 600 µg dose, as soon as practical upon waking each morning prior to breakfast, ideally

at the same time each day. Subjects should be instructed to rotate the injection site around the abdomen. Vials are single-use only, and the subject should be instructed not to re-use the vial after administration of a single dose.

After administration, the used vial, needle and syringe should all be directly discarded in the provided sharps bin. Further details are provided in the home dosing instructions.

Subjects must return any unused investigational product, and the sharps bin, at their next visit to the clinical site. All items can be returned at room temperature.

4.5.1.5 Monitoring of Dose Administration

Monitoring of In-clinic Dose Administration

Injection sites should be routinely examined at each study site visit. If any injection-site reaction meets the criteria for an AE (see Section 5), the event is to be reported on the AE eCRF, with the reaction described as specifically as possible.

As with any biologic product, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

Recording of Daily Dosing and Missed Doses During At-home Dose Administration

Subjects will be instructed to record the date and approximate time of each dose administered at home. If a dose of investigational product is missed, subjects should contact the site, who will contact the medical monitor, for further instructions.

4.5.1.6 Reporting Product Complaints

Any defects with the investigational product must be reported *immediately* to the MedImmune Product Complaint Department by the site with further notification to the site monitor. All defects will be communicated to MedImmune and investigated further with the Product Complaint Department. During the investigation of the product complaint, all investigational product must be stored at labeled conditions unless otherwise instructed.

MedImmune contact information for reporting product complaints:

Email: productcomplaints@medimmune.com

Phone: +1-301-398-2105

Mail: MedImmune
Attn: Product Complaint Department
One MedImmune Way,
Gaithersburg, MD USA 20878

4.5.2 Additional Study Medications

No other study medications are specified for use in this clinical protocol.

4.5.3 Labeling

Labels for the investigational product will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. Label text will be translated into local languages, as required.

4.5.4 Storage

Investigational product must be stored at 2; to 8; in their original container, including during transit to, and storage at, the subject's home. Investigational products do not contain preservatives and are supplied for single-dose use only. Investigational product should be protected from heat and light. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. The label on the investigational product kit specifies the appropriate storage.

4.5.5 Treatment Compliance

Investigational product will be administered at the study site by study site personnel for the 50 µg dose. Subjects are also required to dose at the study site on study day visits when predose assessments are required. Study site personnel will monitor compliance during these visits.

Compliance during the at-home dosing period will be monitored by study site personnel through home-diary review and drug accountability (returned unused vials) at each study visit.

4.5.6 Accountability

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to MedImmune. All unused

investigational product will be returned to a MedImmune-authorized depot or disposed of upon authorization by MedImmune.

For at home dosing periods subjects will be instructed to return any unused vials, and the sharps bin, to the site when they return for their next clinic visits.

4.6 Treatment Assignment and Blinding

4.6.1 Methods for Assigning Treatment Groups

An IWRS will be used for randomization to a treatment group and assignment of blinded investigational product kit numbers. A subject is considered randomized into the study when the investigator notifies the IWRS that the subject meets eligibility criteria and the IWRS provides the assignment of blinded investigational product kit numbers to the subject.

Subjects will be randomized using a 2:1:2:1 ratio to receive either MEDI0382 300 μg or matched placebo, or MEDI0382 600 μg or matched placebo.

Investigational product (MEDI0382 or placebo) must be administered within 24 hours after the investigational product is assigned. If there is a delay in the administration of investigational product such that it will not be administered within the specified timeframe, the study monitor must be notified immediately.

4.6.2 Methods to Ensure Blinding

This is a double-blind study in which MEDI0382 and placebo are identically labeled and indistinguishable in appearance. As such, neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects will be aware of the treatment received (ICH E9).

In the event that treatment allocation for a subject becomes known to the investigator or other study staff involved in the management of study subjects, MedImmune must be notified *immediately*.

4.6.3 Methods for Unblinding

4.6.3.1 Unblinding in the Event of a Medical Emergency

In the event of a medical emergency, the investigator may unblind an individual subject's investigational product allocation. Instructions for unblinding an individual subject's investigational product allocation are contained in the IWRS manual. In general, unblinding should only occur if management of the medical emergency would be different based on the subject having received investigational product. In the majority of cases, the management of a medical emergency would be the same whether or not investigational product was received by the subject. If this was the case, the investigational product allocation should not be unblinded.

In the event there is unblinding, the investigator should promptly document and explain to MedImmune the reason for any premature unblinding.

MedImmune retains the right to unblind the treatment allocation for serious adverse events (SAEs) that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

If a subject's investigational product allocation is unblinded to the blinded staff or blinded MedImmune study team, the subject should be discontinued from investigational product.

4.6.3.2 Unblinding for Interim Analysis Purposes

All personnel involved with the conduct of the study will remain blinded until database lock. The interim analysis will be conducted by an unblinded analysis group comprising statisticians, SAS programmers, and a physician. The results will be reviewed by the Unblinded Review Committee (URC). A limited number of sponsor personnel who are not involved in the conduct of the study will form the URC. Any study team members who have access to the unblinded analyses will not be involved in further conduct of the study. Additional details about the interim analysis and the URC will be provided in the interim analysis charter.

In the event that emergent safety data require it, the sponsor's core cross-functional safety team will have the capacity to introduce an ad-hoc review of unblinded safety data by the URC. The conduct and composition of the URC will be the same as those for the interim analysis. The sponsor's core cross-functional safety team in collaboration with the study statistician and the study physician will decide about the timing and the scope of the ad-hoc review. Analyses will be performed by MedImmune or its representatives. More details will be provided in the statistical analysis plan.

4.7 Restrictions During the Study and Concomitant Treatment(s)

The investigator must be informed as soon as possible about any medication taken from the time of screening until the final study visit. Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF.

4.7.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as "excluded" as listed in Section 4.7.2. Specifically, subjects with T2DM should continue to take their antidiabetic medication (see inclusion criterion 4) at the regular dose prescribed and any other medication prescribed for the treatment of co-morbidities associated with T2DM.

Subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines.

If nausea or vomiting occurs, subjects should be encouraged to reduce oral intake of food until symptoms pass. In the event that symptoms do not improve, subjects should be offered antiemetic therapy in accordance with institutional and local practice guidelines. A centrally acting antiemetic such as a 5HT-3 antagonist is the preferred treatment in the first instance, rather than a prokinetic agent such as domperidone or metoclopramide (Section 3.1.3.1).

Subjects on a stable dose (for at least 1 year) of high dose of vitamin E (> 400 IU) at the time of the baseline biopsy will be permitted to remain on this medication during the course of the study providing no changes are made to the dose (Table 11).

4.7.2 Prohibited Concomitant Medications

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

Use of the following medications will be restricted (Table 11) or prohibited (Table 12) as specified:

Table 11 Restricted medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it's allowed):
Herbal preparations or dietary supplements marketed for control of body weight or appetite	Concurrent or prior use within 1 week prior to the start of screening and during the study
Systemic corticosteroids by oral, intravenous, intra-articular, or intramuscular route	Within 3 months prior to start of screening and during the study unless prescribed for a very brief period of less than 7 days
Vitamin E (high doses > 400 IU)	Concurrent use, unless on a stable dose for at least 1 year prior to baseline biopsy and no changes made during study. Vitamin E must not have been initiated after the baseline liver biopsy was performed.
Pioglitazone or other PPAR-γ agonists	Concurrent use, unless on a stable dose for at least 1 year prior to baseline biopsy, and no changes made during study
Domperidone and metoclopramide	Only to be used during the study for the treatment of nausea and vomiting in the instance of intolerance to a centrally-acting anti-emetic
Insulin	Only to be used for treatment of severe hyperglycemia as rescue medication and according to local guidelines

IU = International units, PPAR-γ = Peroxisome proliferator-activated receptor gamma

Table 12 Prohibited medications

Prohibited medication/class of drug:	Usage
Therapies associated with development of NAFLD such as methotrexate, tamoxifen, amiodarone, or long-term use of tetracyclines	Within 3 months of baseline biopsy until the end of the study. In the case of tetracyclines, these drugs are restricted during the study unless prescribed for a very brief period of less than 7 days
Therapies in classes under investigation for the treatment of NASH (except for SGLT-2 inhibitors and PPAR-γ agonists), such as obeticholic acid	Within 3 months of baseline biopsy until the end of the study
GLP-1 receptor agonists and GLP-1 receptor agonist containing therapies	Within 3 months of baseline biopsy until the end of the study
Drugs approved for weight loss (eg, orlistat, bupropion/naltrexone, phentermine-topiramate, phentermine, lorcaserin), as well as those drugs used off-label	Concurrent or previous use within the last 3 months prior to the start of screening and during the study

GLP-1 = glucagon-like peptide-1; NAFLD = Non-alcoholic fatty liver disease; NASH = Non-alcoholic steatohepatitis; PPAR-γ = Peroxisome proliferator-activated receptor gamma; SGLT-2 = Sodium-glucose co-transporter 2

4.8 Statistical Evaluation

4.8.1 General Considerations

In general, data will be provided in listings and tabular summaries. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics, including mean, standard deviation (SD), median, minimum, and maximum. Baseline values will be defined as the last assessment prior to the first administration of investigational product. Additional details will be described in the statistical analysis plan.

4.8.2 Sample Size

The primary objective of the study is safety, but sample size and power are calculated on pharmacodynamic endpoint HFF. Assuming 20% treatment difference on percent change in HFF with SD = 20%, and assuming a 25% dropout rate, 24 subjects per group will provide about 83% power to detect a treatment difference between a MEDI0382 group and the placebo (alpha = 0.05, 2-sided). No multiplicity adjustment for alpha is planned.

4.8.3 Efficacy

4.8.3.1 Efficacy Analysis

The efficacy analyses will be based on the Intent-to-treat population.

The pharmacodynamic endpoint, percent change from baseline in HFF at Week 19, is an efficacy endpoint for the study. The percent change from baseline to Week 19 in HFF will be analyzed using analysis of covariance (ANCOVA) adjusting for treatment and baseline value. For the other pharmacodynamic and biomarker endpoints that are continuous variables, similar ANCOVA analyses as the above analysis will be carried out. For ANCOVA analyses, last observation carried forward (LOCF) method will be applied for efficacy endpoints to handle missing data, that is, a missing endpoint will be replaced with the last available post-baseline measurement prior to the missing endpoint.

4.8.3.2 Additional Analyses of the Efficacy Endpoint

The sensitivity analysis 1 will be conducted on the percent change from baseline to Week 19 in HFF using a mixed model for repeated measures approach under unstructured covariance structure including fixed effects of treatment, visit, and treatment-by-visit interaction as well as covariate of baseline.

The sensitivity analysis 2 will consist of conducting Wilcoxon sum-rank test on percent change from baseline in HFF at Week 12 and Week 19 for all treatment groups.

The sensitivity analysis 3 will consist of repeating the descriptive analysis and the ANCOVA model on the same population used for the main analysis but including only data in the on-treatment phase. It is performed at interim analysis and at final analysis.

The sensitivity analysis 4 consists on repeating the descriptive analysis and the ANCOVA model on the Per-protocol population. It is performed at interim analysis and at final analysis.

4.8.4 Safety

4.8.4.1 Analysis of Adverse Events

Safety analyses will be based on As-treated population. Treatment-emergent AEs and SAEs will be coded by the most updated version of the Medical Dictionary for Regulatory Activities (MedDRA), and the type, incidence, severity and relationship to study investigational product will be summarized by MedDRA System Organ Class and Preferred Term and by treatment. Specific AEs will be counted once for each subject for calculating percentages. In addition, if the same AE occurs multiple times within a subject, the highest severity and level of relationship observed will be reported.

Other safety data, such as vital signs, clinical laboratory data, and dECG will be descriptively summarized at each time point by treatment.

4.8.4.2 Analysis of Clinical Laboratory Parameters

Laboratory parameters will be assessed at baseline as well as throughout the study. Laboratory parameters will be assessed by presenting tables containing information related to laboratory shifts from baseline relative to the normal range, as well as descriptively over time.

Hepatic safety analyses:

- Proportion of subjects with marked changes (5 × ULN, 8 × ULN) from baseline in ALT and AST
- Mean changes from baseline to end of treatment in ALT and AST levels

4.8.5 Analysis of Immunogenicity/Pharmacokinetics

Subjects who have at least one measurable concentration time point of investigational product will be used for this analysis.

Pharmacokinetic parameters such as, but not limited to, C_{max}, time to maximum observed plasma drug concentration (t_{max}), and AUC, per group on the last day of dosing, may be estimated from plasma concentration-time data for MEDI0382 if data permit. Descriptive statistics will be generated for pharmacokinetic parameters for MEDI0382 in group. Additional summary statistics on predose concentrations and specific postdose concentrations may be listed, if data permits, by group, treatment and day and will be summarized as maximum, minimum, arithmetic mean, and geometric mean.

The number and percentage of subjects with confirmed positive serum antibodies to MEDI0382 will be reported by dose level and titer data will be summarized descriptively. The potential impact of ADA on MEDI0382 pharmacokinetics, efficacy and safety will be evaluated.

ADA incidence rate and titer will be tabulated by treatment. Samples confirmed positive for ADA will be analyzed for titer and reported.

4.8.6 Interim Analysis

An interim analysis is planned after approximately 39 subjects have completed approximately 19 weeks of treatment.

The purpose of this interim analysis is to help inform further clinical development; no changes will be made to this study unless a safety signal is observed. The interim analysis will be described in the interim analysis charter. The interim analysis results will not be provided to the investigator.

5 ASSESSMENT OF SAFETY

5.1 Definition of Adverse Events

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

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

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline is not considered an AE (serious or non-serious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

5.2 Definition of Serious Adverse Events

An SAE is any AE that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in offspring of the subject
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

5.3 Recording of Adverse Events

AEs will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. AEs will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an

SAE and therefore requires immediate notification to MedImmune (see Section 5.4). See Section 5.2 for the definition of SAEs and Appendix B for guidelines for assessment of severity and relationship.

If an AE evolves into a condition that meets the regulatory definition of "serious," it will be reported on the SAE Report Form.

5.3.1 Time Period for Collection of Adverse Events

SAEs will be collected from time of signature of informed consent, throughout the treatment period and including the follow-up period.

AEs will be recorded from time of first dose of investigational product, throughout the treatment period and including the follow-up period.

5.3.2 Follow-up of Unresolved Adverse Events

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

5.3.3 Deaths

All deaths that occur during the study, including the protocol-defined follow-up period must be reported as an SAE.

5.3.4 Adverse Events Based on Signs and Symptoms

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

5.3.5 Adverse Events Based on Examination and Tests

The results from the protocol-mandated laboratory tests and vital signs will be summarized in the CSR. An abnormal laboratory finding (including dECG finding) that requires medical intervention by the investigator, or a finding judged by the investigator as medically significant should be reported as an AE. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure,

hematuria) not the laboratory abnormality (eg, elevated creatinine, urine red blood cell increased)

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

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

5.3.6 Potential Hy's Law and Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN will need to be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

5.4 Reporting of Serious Adverse Events

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

If any SAE occurs in the course of the study, then investigators or other site personnel must inform the appropriate sponsor representative(s) within 1 day, ie, immediately but no later than 24 hours after becoming aware of the event.

The designated study representative works with the investigator to ensure that all the necessary information is provided to the sponsor's Patient Safety data entry site within 1 calendar day of initial receipt for fatal and life-threatening events and within 5 calendar days of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform sponsor representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but no later than 24 hours after becoming aware of the event.

Once the investigators or other site personnel indicate an AE is serious in the eCRF, an automated email alert is sent to inform the designated sponsor representative(s).

If the eCRF is not available, then the investigator or other study site personnel reports an SAE to the appropriate sponsor representative by telephone. The sponsor representative will advise the investigator/study site personnel how to proceed.

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

5.5 Other Events Requiring Immediate Reporting

5.5.1 Overdose

An overdose is defined as a subject receiving a dose of investigational product in excess of that specified in the IB, unless otherwise specified in this protocol.

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

If an overdose on a MedImmune investigational product occurs during the course of the study, then the investigator or other site personnel should inform appropriate sponsor representatives immediately, but no later than 24 hours after becoming aware of the event.

The designated sponsor representative works with the investigator to ensure that all relevant information is provided to the sponsor's Patient Safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply; see Section 5.4. For other overdoses (ie, those not associated with an AE or SAE), reporting must occur within 30 days.

5.5.2 Pregnancy

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

- If the pregnancy is discovered before the study subject has received any investigational product.
- Pregnancies in the partner of male subjects.

5.5.2.1 Maternal Exposure

If a subject becomes pregnant during the course of the study investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication.

Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs during the course of the study, then the investigator or other site personnel will inform the appropriate sponsor representatives within 1 day, ie, immediately but **no later than 24 hours** after becoming aware of the event.

The designated study representative works with the investigator to ensure that all relevant information is provided to the sponsor's Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 5.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The pregnancy reporting module in the eCRF is used to report the pregnancy and the pregnancy outcome module is used to report the outcome of the pregnancy.

5.5.3 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for a MedImmune investigational product that either causes harm to the subject or has the potential to cause harm to the subject.

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

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the subject received the drug
- Did not occur, but circumstances were recognized that could have led to an error

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

- Drug name confusion (ie, instead of receiving the investigational product, the subject received a drug that has a similar-sounding name)
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the subject
- Drug not administered as indicated, for example, wrong route or wrong site of administration

- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature
- Wrong subject received the medication (excluding IWRS errors)
- Wrong drug administered to subject (excluding IWRS errors)

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

- Errors related to or resulting from IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Subject accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Subject failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ or MedImmune product

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

If a medication error occurs in the course of the study, then the investigator or other site personnel informs the appropriate MedImmune representatives within 1 day, ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated MedImmune representative works with the investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 5.4) and within 30 days for all other medication errors. Medication errors should be reported using a Medication Error Report Form.

6 STUDY AND DATA MANAGEMENT

6.1 Training of Study Site Personnel

Before the first subject is entered into the study, a MedImmune representative will review and discuss the requirements of the protocol and related documents with the investigational staff and also train them in any study-specific procedures and system(s) utilized.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

6.2 Monitoring of the Study

During the study, a MedImmune representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that investigational product accountability checks are being performed.
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts).
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The MedImmune representative will be available between visits if the investigator(s) or other staff at the site needs information and advice about the study conduct.

6.2.1 Source Data

Refer to the Clinical Study Agreement (CSA) for location of source data.

6.2.2 Study Agreements

The Principal Investigator at each/the site should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this protocol and the CSA, the terms of protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the CSA shall prevail.

Agreements between MedImmune and the Principal Investigator must be in place before any study-related procedures can take place, or subjects are enrolled.

6.2.3 Archiving of Study Documents

The investigator follows the principles outlined in the CSA.

6.3 Study Timetable and End of Study

An individual subject will be considered to have completed the study if the subject was followed through their last protocol-specified visit/assessment or assessed for the primary end point of the study, regardless of the number of doses of investigational product that was received.

Subjects will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow-up (see Section 4.1.6 and Section 4.1.7).

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study.

6.4 Data Management

Data management will be performed by MedImmune Data Management staff or other party according to the Data Management Plan.

An eCRF will be used for data collection and query handling. The investigator will ensure that data are recorded in the eCRFs as specified in the study protocol and in accordance with the eCRF instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the CSA. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

6.5 Medical Monitor Coverage

Each subject will be provided with contact information for the Principal Investigator. In addition, each subject will receive a telephone number intended to provide the subject's physician access to a medical monitor 24 hours a day, 7 days a week in the event of an emergent situation where the subject's health is deemed to be at risk. In this situation, when a subject presents to a medical facility where the treating physician or health care provider requires access to a physician who has knowledge of the investigational product and the clinical study protocol and the Principal Investigator is not available, the treating physician or health care provider can contact a medical monitor through this system, which is managed by a third party vendor.

7 ETHICAL AND REGULATORY REQUIREMENTS

7.1 Subject Data Protection

Each subject will be assigned a E-code to ensure that personally identifiable information is kept separate from the study data. Subject data that are relevant to the study, eg, demographic

information, physical or mental health condition, diagnosis, comorbidities, laboratory test results, etc. will only be collected with the subject's informed consent. The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that describes how subject data will be collected, used, and distributed in compliance with relevant data protection and privacy legislation. Data (clinical and biological sample) from this study may be used and may be combined with results from other studies for additional scientific-related research, based on agreement from the subject as defined in the informed consent.

Extra precautions will be taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. MedImmune will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law**.**

7.2 Ethics and Regulatory Review

The IRB/IEC responsible for each site must review and approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the subjects. The IRB/IEC must also approve all advertising used to recruit subjects for the study. The investigator is responsible for submitting these documents to the applicable IRB/IEC and distributing them to the study site staff.

The opinion of the IRB/IEC must be given in writing. The investigator must provide a copy of the written approval to MedImmune before enrolment of any subject into the study.

MedImmune should approve any substantive modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol must be re-approved by the IRB/IEC annually.

Before the study is initiated, MedImmune will ensure that the national regulatory authority in each country has been notified and their approval has been obtained, as required. MedImmune will provide safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions where relevant, to regulatory authorities, IRB/IEC, and principal investigators.

Each Principal Investigator is responsible for providing reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product to the IRB/IEC. MedImmune will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

7.3 Informed Consent

Informed consent of each subject will be obtained through a written and verbal explanation process that addresses all elements required by ICH/GCP. MedImmune will develop a core ICF for use by all investigators in the clinical study. MedImmune must approve any modifications to the ICF that are needed to meet local requirements.

The Principal Investigator(s) at each site will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF is stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the ICF that is approved by an IRB/IEC

7.4 Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and MedImmune. Any changes must be documented in a study protocol amendment.

For a substantial change to the protocol, MedImmune will distribute amended versions of the protocol to the Principal Investigator(s). Before implementation, amended protocols must be approved by relevant IRB/IEC (see Section 7.2) and reviewed as per local regulatory authority requirements. The IRB/IEC must also approve revisions to the ICF, advertising, and any other written information and/or materials resulting from the change to the protocol.

Any non-substantial changes will be communicated to or approved by each IRB/IEC.

7.5 Audits and Inspections

Authorized representatives of MedImmune, a regulatory authority, or an IRB/IEC may perform audits or inspections at the site, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the

International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact MedImmune immediately if contacted by a regulatory agency about an inspection at the site.

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9 CHANGES TO THE PROTOCOL

9.1 Protocol Amendment 6

The following change has been incorporated into the current version, considered Protocol Amendment 6, of the protocol.

The change is considered non-substantial.

Title page: The medical monitor was changed from PPD to PPD.

9.2 Protocol Amendment 5

All changes described below have been incorporated into the current version of the protocol.

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 5. All changes made to the body of the protocol have been reflected in the Protocol Synopsis. Editorial mistakes have been corrected and are not noted below.

The following change is considered substantial:

1. Section 3.1.1 (Overview) and Section 4.8.6 (Interim Analysis): to improve the distribution of subjects with a sufficient range of disease to be included in the interim

analysis, the timeframe was changed from 13 weeks to 19 weeks of completed treatment for approximately 39 subjects (a change from 30 subjects).

The following changes are considered non substantial:

2. Table 5 (Screening Schedule of Procedures) Footnote 'f' and Section 4.3.5.1 (Magnetic Resonance Imaging [Including MRI-PDFF]): to allow for repeat screening MRI the following text was added '*If the screening MRI is determined to be of inadequate image quality by the MRI analysis vendor the subject may return for repeat MRI within the screening visit period*'.

3. Section 4.2.2 (Randomized Treatment Period): to maintain subject safety, and to allow for continued data collection during the COVID-19 pandemic, text was added to allow for telephone contact where study visits are not possible, to allow D78 MRI to be collected at the earliest opportunity and within 7 days of the original D78 scheduled date, and to allow D133 assessments to be collected within a 2 days window (7 days for MRI), and if 2 days are not possible, to be collected at the earliest opportunity and within 7 days, excluding pharmacokinetic blood, of the original D133 scheduled date. It is noted that all other visits should follow the original schedule.

9.3 Protocol Amendment 4

All changes described below have been incorporated into the current version of the protocol.

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 4. All changes made to the body of the protocol have been reflected in the Protocol Synopsis. Editorial mistakes have been corrected and are not noted below.

The following changes are considered substantial:

Body weight, although collected, was not described as a specific objective in the original protocol. Body weight changes are an important parameter for the assessment of MEDI0382 in NASH and therefore body weight and BMI have been called out as a distinct objective and included as a dose response endpoint.

1 Table 2 (Secondary Objectives and Associated Endpoints): change in body weight and BMI added as a new secondary objective.
2 Table 2 (Secondary Objectives and Associated Endpoints): body weight added to the dose response endpoints.

Due to the nature of the study population, some subjects will be receiving prescribed medication which could result in a positive screen for drugs of abuse. However, where medication is prescribed and does not indicate an addiction or safety concern the Investigator

is permitted to include the subject at their discretion. Exclusion Criterion 14 was amended as follows:

3 Section 4.1.3 (Exclusion Criteria): reworded from *History of substance dependence likely to impact subject safety or compliance with study procedures, or positive screen for drugs of abuse at screening* to *History of substance dependence or a positive screen for drugs of abuse, likely to impact subject safety or compliance with study procedures, at the discretion of the Investigator.*

The following changes are considered non-substantial:

4 Table 2 (Secondary Objectives and Associated Endpoints): *liver sagittal diameter* and *liver transversal diameter* changed to *abdominal sagittal diameter* and *abdominal transversal diameter*.

[redacted]

Section 4.8.6 (Interim Analysis): *interim unblinding analysis plan* changed to *interim analysis charter.*

9 Section 3.1.3.3 (Persistent Hyperglycemia): DPP-4i should be avoided and alternative options considered.

10 Section 3.2.3 (Rationale for Endpoints): rationale for the addition of body weight and BMI to secondary endpoints.

11 Section 4.1.5 (Screen Failures): text added to clarify that the same E-code will be used for subjects who are rescreened.

12 Section 4.1.8 (Study Stopping Criteria): clarification to text due to site feedback.

13 Table 5 (Screening Schedule of Procedures):

- ∀ Clarification that virology at a minimum includes hepatitis B surface antigen, hepatitis C virus antibody; HIV-1 and HIV-2
- ∀ Footnote ‘c’: clarification that screening dECG measurements should be performed after the subject has rested in the supine position for *at least* 10 minutes.

- ∀ Footnote ‘f’: *MRI (including MRI-PDFF)* changed to *MRI-PDFF*. Change implemented to avoid confusion regarding which screening MRI protocol should be used.
- ∀ Footnote ‘i’: text added to confirm that if multiple alcohol screening tests are performed and conflicting results occur any positive result should be documented.

14 Table 6 (MEDI0382/Matched Placebo 300 µg Treatment Period Schedule of Procedures) and Table 7 (MEDI0382/Matched Placebo 600 µg Treatment Period Schedule of Procedures) footnotes ‘f’ and ‘g’: to allow for flexibility, dECG and vital sign predose collection times changed to allow assessments *within* 20 minutes, respectively.

15 Table 8 (Schedule of Follow-up Procedures) footnote ‘b’: the requirement for a HbA1c sample for subjects requiring an ADA follow-up sample was removed. This assessment is not required to interpret the immunogenicity profile during safety follow-up.

16 Section 4.3.2.4 (Vital Signs): to allow flexibility, it was clarified that blood pressure should be performed after the subject has rested in the supine position for *at least* 10 minutes.

17 CCI [redacted]

18 Section 4.3.5.2 (Fibroscan): *according to the Imaging Manual* removed because this is inaccurate.

19 Section 4.3.6 (Clinical Laboratory Tests): nitrites added, as they were previously omitted from the urinalysis tests. Low molecular weight adiponectin removed to reflect laboratory standard practice.

20 CCI [redacted]

21 Section 4.5.1.6 (Reporting Product Complaints): telephone and fax numbers removed to reflect organisational changes.

22 Section 4.6.3.2 (Unblinding for Interim Analysis Purposes): text updated to reflect the unblinding plans. Specifically, the following text was added: *The conduct and composition of the URC will be the same as those for the interim analysis. The sponsor’s core cross-functional safety team in collaboration with the study statistician and the study physician will decide about the timing and the scope of the ad-hoc review.*

23 Section 4.8.3.2 (Additional Analyses of the Efficacy Endpoint): additional sensitivity analyses of the efficacy endpoint were added.

24 Section 6.5 (Medical Monitor Coverage): clarification to the text that the telephone number will not be toll-free.

25 Appendix E (Genetic Research): changes made to informed consent description to clarify that a single informed consent document will be used during the study. This single document enables a subject to decide whether to be included in the optional genetic and non-genetic samples.

9.4 Protocol Amendment 3

All changes described below have been incorporated into the current version of the protocol.

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 3.

All changes are considered non-substantial and that there are no substantial changes.

1 Section 3.1.1 (Overview): the study flow diagram was corrected to accurately reflect the numbers of subjects per group.
2 Section 4.1.3 (Exclusion Criteria): criterion 32 incorrectly included, text is for information only, criterion numbering has been removed.
3 Section 4.1.6 (Withdrawal from the Study) and Section 4.1.7 (Discontinuation of Investigational Product): clarification to text to specify that subjects who discontinue early, but are not continuing with study assessments, should in addition to the Early Discontinuation Visit return for a follow-up visit. Text regarding 3 MRIs was also clarified.
4 Section 4.3.5.1 (Magnetic Resonance Imaging [Including MRI-PDFF]) and Section 4.3.5.2 (Fibroscan): Table 8 added as a cross reference.
5 Table 6 (MEDI0382/Matched Placebo 300 µg Treatment Period Schedule of Procedures), Table 7 (MEDI0382/Matched Placebo 600 µg Treatment Period Schedule of Procedures), Section 4.5.1.3 (Dose Preparation Steps), Table 10 (MEDI0382 and Placebo Dose Preparation) and Section 4.6.2 (Methods to Ensure Blinding): to mitigate the need for unblinded study personnel the 50 µg matched placebo dose will now require dilution. Text stating that placebo does not require dilution and text describing unblinded study personnel has been removed.
6 Table 8 (Schedule of Follow-up Procedures):
   (a) Footnote ‘e’ updated to specify that subjects who discontinue early, but are not continuing with study assessments, should also return for a follow-up visit.
   (b) Clarification added to footnote ‘f’ to clarify that only 3 MRIs should be completed per subject.
   (c) Footnote ‘g’ added to clarify the timing of the pharmacokinetic sample.
7 Appendix D (Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy’s Law): to the lab kit table the requirement for IgM anti-HCV testing was removed and a footnote added to confirm when HCV RNA testing is required.

9.5 Protocol Amendment 2

All changes described below have been incorporated into the current version of the protocol.

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 2. All changes made to the body of the protocol have been reflected in the protocol synopsis. For consistency EDC was changed to eCRF and SID to E-code throughout the protocol and any reference to a CRO was removed.

Changes to the protocol considered substantial are:

1 Section 2.2 (Secondary Objective and Associated Endpoints): 'percent change' added to the pharmacodynamics endpoints for clarification.

2 CCI [redacted]

3 Section 4.1.6 (Withdrawal from the Study) and 4.1.7 (Discontinuation of Investigational Product): text added to clarify the process in the event of a subject withdrawal. If only the investigational product is withdrawn but the subjects continues they should complete an Early Discontinuation visit and if possible all scheduled assessments, however, if the subject wishes to withdraw completely the investigator should ask them to return for an Early Discontinuation Visit. The number of MRI should not exceed 3 for any subject randomized into the study

4 Table 6 (MEDI0382/Matched Placebo 300 µg Treatment Period Schedule of Procedures):
   (a) HbA1c and fasting lipid profile assessments added to D78.
   (b) Adiponectin assessments added to D1, D78, and D133.

5 Table 7 (MEDI0382/Matched Placebo 600 µg Treatment Period Schedule of Procedures):
   (a) HbA1c and fasting lipid profile assessments added to D78.
   (b) Adiponectin assessments added to D1, D78, and D133.

6 Table 8 (Schedule of Follow-up Procedures):
   (a) Calcitonin assessment added with corresponding footnote.
   (b) Assessments, and corresponding footnote, for IP accountability, fasting MRI-PDFF (including specification to not exceed 3 MRI following randomization), fibroscan, and pharmacokinetics added for those subjects completing the Early Discontinuation Visit.
   (c) Footnoted the requirement for HbA1c to be taken to evaluate the subjects glycemic control.

7 CCI [redacted]

8 Section 4.3.12 (Estimate of Volume of Blood to be Collected): total blood volumes were updated to reflect additional sampling, approximately 461 mL, plus an optional 60 mL for the MEDI0382 300 µg/matched placebo group and 557 mL, plus an optional 60 mL for the MEDI0382 600 µg/matched placebo group.

9 Section 5.3.1 (Time Period for Collection of Adverse Events) and Table 5: in the previous amendment AEs and SAEs were to be collected from signed informed consent and first dose of investigational product. This has been changed to only SAEs to be collected from signed informed consent and first dose of investigational product.

Changes considered minor are provided below:

10 Section 3.1.1 (Overview): the study flow diagram was updated to include the run-in period with accompanying footnote and total treatment duration.

11 Section 3.1.1 (Overview) and (Interim Analysis): interim analysis text updated to say ’30 subjects have completed approximately 13 weeks of treatment’

12 Section 4.1.2 (Exclusion Criteria): exclusion criterion 30 changed from *Any AstraZeneca, MedImmune, contract research organization (CRO), or study site employee, or close relatives of any of the aforementioned employees* to *Any AstraZeneca, MedImmune, or study site employee, or close relatives of any of the aforementioned employees.* The update was made to reflect organizational changes.

13 Section 4.1.4 (Subject Enrollment and Randomization), Table 5: SID number changed to E-code for consistency.

14 New Section 4.1.5 (Screen Failures): section added to clarify how screening failures will be handled during the study.

15 Section 4.3.2.2 (Physical Examination): text changed to clarify that clinically significant physical examination findings should be recorded as AEs.

16 Section 4.3.2.3 (Digital Electrocardiogram): ‘data’ removed for clarification. The investigators are not expected to input data into the dECG, the data will be transferred directly. For the variables to be reported, RR was removed and HR and QTcB were added in order to align the text with the data to be collected at the site.

17 Section 4.3.6 (Clinical Laboratory Tests): the following tests were added to the additional laboratory assessments: adiponectin, lipidomics, ELF™, and CK18. Only adiponectin is an additional test, all other tests were included in the previous version of the protocol and have been added here for clarity. Adiponectin is an important lipid parameter for NASH.

18 Table 5 (Screening Schedule of Procedures): an additional check of eligibility criteria was added at V2.

19 Table 6 (MEDI0382/Matched Placebo 300 µg Treatment Period Schedule of Procedures):
   (a) Requirement for height measurement at D133 removed.
   (b) IP accountability assessment added.
   (c) The term ‘future samples for testing’ removed from lipidomics, CK18, and Elf™ assessments.
   (d) Serum lipid profile changed to lipid profile.

20 Table 7 (MEDI0382/Matched Placebo 600 µg Treatment Period Schedule of Procedures):
   (a) Requirement for height measurement at D133 removed.
   (b) IP accountability assessment added.
   (c) The term ‘future samples for testing’ removed from lipidomics, CK18, and Elf™ assessments.
   (d) Changes made to footnote ‘h’ to make BP collection consistent with main body.
   (e) Serum lipid profile changed to lipid profile.

21 Table 8 (Schedule of Follow-up Procedures):
   (a) Requirement for height measurement removed.
   (b) Serum lipid profile changed to lipid profile.
   (c) IP accountability assessment added.

22 Section 4.8.3.2 (Additional Analyses of the Efficacy Endpoint): the ANCOVA analysis was removed as this analysis is already discussed in Section 4.3.8.1.

23 Appendix B (Adverse Event Definitions and Additional Safety Information): updated to reflect operational changes affecting AE reporting.

9.6 Protocol Amendment 1

All changes described below have been incorporated into the current version of the protocol.

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 1. All changes made to the body of the protocol have been reflected in the Protocol Synopsis.

The principal reason for this amendment was to incorporate feedback from the US FDA to improve safety monitoring.

Changes, made in response to US FDA guidance, are considered substantial and are as follows:

1 Section 4.1.3 (Exclusion Criteria): new exclusion criterion 9 added: 'Physician-diagnosed diabetic subjects with clinically significant gastroparesis (as judged by the investigator) or those treated for gastroparesis within 6 months prior to screening'.

2 Section 4.1.3 (Exclusion Criteria): exclusion criterion 25 (f) changed from 'Platelets < 100×10^9/L' to 'Platelets < 140-150,000/mm^3'.

3 Table 5 (Screening Schedule of Procedures): an extra visit was added to screening to accommodate ABPM (and corresponding footnote) at -10 days ± 3 days.

4 Table 7 (MEDI0382/Matched Placebo 600 μg Treatment Period Schedule of Procedures):
   (a) Six additional visits at Days 51, 52, 65, 66, 79, and 80 added at 24 and 48 hours after uptitration to 400, 500 and 600 μg, respectively.
   (b) Postural BP specified at Visits 9 (Day 51), 10 (Day 52), 12 (Day 65), 13 (Day 66), 15 (Day 79) and 16 (Day 80) with accompanying explanatory footnote.
   (c) ABPM added to Visits 8 (Day 50), 11 (Day 64), 14 (Day 78), and 20 (Day 133).
   (d) Extra sampling was added for plasma glucose, insulin, glucagon, c-peptide, and GLP-1 at Visits 8 (Day 50), 9 (Day 51), 10 (Day 52), 11 (Day 64), 12 (Day 65), 13 (Day 66), 15 (Day 79), and 16 (Day 80).

5 Section 4.3.2.4 (Vital Signs): clarification and new text added to allow for postural BP and ABPM measures at time points specified in Table 7. Section also added to provide details regarding training for the application and wearing of the ABPM device.

6 Section 4.6.3.2 (Unblinding for Interim Analysis Purposes): clarification added that the sponsor's core cross-functional safety team have the capacity to introduce an earlier, ad-hoc review of unblinded safety data by the URC in the event that emergent safety data require it.

Further changes, to improve safety monitoring and endpoint reporting, and to correct minor errors were also implemented. It should be noted that visit numbers have been updated throughout the protocol to reflect additional visits, however, the overall time period of the study was not changed.

Additional changes to the protocol considered to be substantial are summarized below:

7 Section 1.6 (Benefit-risk and Ethical Assessment): section updated to align with most recent edition of the IB.

8 Section 2.1 (Primary Objectives and Associated Endpoints): clarifications made to primary endpoint wording. Changes made to allow to allow standard reporting on clinicaltrials.gov. All other safety endpoints will be reviewed and detailed in the statistical analysis plan.

9 Section 2.1.1 (Secondary Objectives and Associated Endpoints): clarifications made to the other related imaging parameters secondary objective and endpoint wording. PDFF deleted from MRI, CCI

10 Section 3.1.1 (Overview) and Section 4.8.6 (Interim Analysis): 'interim analysis of safety data'/'interim safety analysis'/'safety interim analysis' was considered too restrictive, therefore, 'safety data'/'safety' was removed. The interim analysis will be described in the interim analysis unblinding plan.

11 Section 3.1.3.1 (Tolerability): addition of instructions for investigators to monitor subjects with vomiting for signs of hypovolemia and instructions regarding hydration for subjects with impaired renal function.

12 Section 3.1.3.2 (Hypoglycemia): text clarified to confirm glucose reading and hypoglycemic events will be reviewed and managed by the investigator as per local standards of care and that glucose meters will be provided to subjects with T2DM.

13 Table 5 (Screening Schedule of Procedures):
   (a) MRI (including MRI-PDFF) and fibroscan moved to new Visit 2 at -10 days to maintain the timeframe between these procedures and randomization.
   (b) Footnote added to confirm historical MRI (including MRI-PDFF)/fibroscan assessments can be used for screening procedures.

14 Table 6 (MEDI0382/Matched Placebo 300 µg Treatment Period Schedule of Procedures):
   (a) dECG and vital sign measures on Days 50, 64, and 78 were deleted, to reduce subject burden.
   (b) Footnote to clarify dosing added: Subjects are required to be dosed at the clinic for the 50 µg dose and on all study day visits when predose procedures are required. Subjects are required to fast for at least 8 hours overnight prior to Visits 3 (Day 1), 10 (Day 78) and 14 (Day 133); subjects are permitted to drink water during this period of fasting. On days where subjects attend the clinic in a fasted state, blood and urine samples should be obtained prior to administration of investigational product.
   (c) On Visit 20 (Day 133), the 12-hour pharmacokinetic sampling time point was changed to 10 hours to make sampling easier for the subject.

15 Table 7 (MEDI0382/Matched Placebo 600 µg Treatment Period Schedule of Procedures):

(a) Footnote to clarify dosing added: Subjects are required to be dosed at the clinic for the 50 µg dose and on all study day visits when predose procedures are required. Subjects are required to fast for at least 8 hours overnight prior to Visits 3 (Day 1), 14 (Day 78) and 20 (Day 133); subjects are permitted to drink water during this period of fasting. On days where subjects attend the clinic in a fasted state, blood and urine samples should be obtained prior to administration of investigational product. Subjects are required to visit the clinic on two subsequent days following up-titration to the 400, 500 and 600 µg dose for safety monitoring; subjects may travel to the site for daily visits during this time or alternatively should be given the option to stay overnight locally if this is more convenient.

(b) To monitor subject safety, extra sampling was added for serum chemistry at Visits 8 (Day 50), 9 (Day 51), 10 (Day 52), 11 (Day 64), 12 (Day 65), 13 (Day 66), 15 (Day 79), and 16 (Day 80).

(c) On Visit 20 (Day 133), the 12-hour pharmacokinetic sampling time point was changed to 10 hours to make sampling easier for the subject.

16 CCI

17 CCI

18 Section 4.3.12 (Estimate of Volume of Blood to be Collected): total blood volumes were updated to reflect additional sampling, approximately 389.4 mL, plus an optional 81.4 mL for the MEDI0382 300 µg/matched placebo group and 480.4 mL, plus an optional 81.4 mL for the MEDI0382 600 µg/matched placebo group.

Changes to the protocol considered to be non-substantial are summarized below:

19 To reflect organizational changes Covance was removed from the title page.

20 Section 4.1.2 (Inclusion Criteria 6): Added clarification that the MRI assessment should be PDFF, and that an historical MRI-PDFF can be used for the screening hepatic steatosis or liver fat assessment.

21 Table 5 (Screening Schedule of Procedures), Table 7 (MEDI0382/Matched Placebo 600 µg Treatment Period Schedule of Procedures): AE and concomitant medication monitoring included in the extra visits during this amendment.

22 Table 6 (MEDI0382/Matched Placebo 300 µg Treatment Period Schedule of Procedures): NIS4 sample removed from Week 2, as this was incorrectly included in the original protocol.

23 Table 6 (MEDI0382/Matched Placebo 300 µg Treatment Period Schedule of Procedures) and Table 7 (MEDI0382/Matched Placebo 600 µg Treatment Period Schedule of Procedures): for clarity 'dispense glucose meter' added with accompanying footnote.

24 Table 7 (MEDI0382/Matched Placebo 600 µg Treatment Period Schedule of Procedures): footnote 'g', regarding vital signs, which was missing from the original protocol was added.

25 Table 8 (Schedule of Follow-up Procedures):

(a) footnote 'a' deleted from ADA, this was incorrectly included in the original protocol.

(b) Clarification added to new footnote 'a' to confirm consecutive measurements are for BP only.

26 Section 4.3.2.5 (Weight, Height, BMI, Waist and Hip Circumference): clarification to confirm height recorded at screening will be used for eligibility assessment, and height recorded at Visit 3 (Day 1) will be used for subsequent BMI calculations.

27 Section 4.3.5.1 (Magnetic Resonance Imaging (including MRI-PDFF): CCI [redacted] Added clarification that subjects with an MRI performed within 60 days of screening do not need to repeat this assessment at Visit 2 (Day -10).

28 Section 4.3.5.2 (Fibroscan): added clarification that subjects with a fibroscan performed within 60 days of screening do not need to have a fibroscan performed at Visit 2 (Day -10).

29 Section 4.5.1.3 (Dose Preparation Steps): clarification added Table 10 (MEDI0382 and Placebo Dose Preparation).

30 Section 4.5.4 (Storage): clarification added to confirm storage conditions for transit to and storage at the subject's home.

31 Section 4.7.1 (Permitted Concomitant Medications): screening biopsy deleted as no screening biopsy will be taken in this study; historical biopsy changed to baseline biopsy for consistency.

32 Appendix E (Genetic Research): clarification that sample will only be taken on Visit 3 (Day 1), not at any timepoint as incorrectly included in the original protocol.

Appendix A Contraception Guidance

For females of childbearing potential:

- Females of childbearing potential are defined as those who are not surgically sterile (ie, surgical sterilization includes bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or those who are not premenarchal or postmenopausal defined as 12 months with no menses without an alternative medical cause and have an elevated follicle-stimulating hormone [FSH] central laboratory level > 40 mIU/mL). FSH testing will be conducted at the screening visit to confirm postmenopausal status).
- A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The acceptable methods of contraception are described in Table A1.
- Female subjects must refrain from egg cell donation and breastfeeding while on study and for 28 days after the final dose of investigational product.

Table A1 Highly Effective Methods of Contraception

Barrier Methods	Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system or implant; eg, Mirena®) [a]	• Implants • Hormone shot or injection • Combined pill • Minipill • Patch

[a] This is also considered a hormonal method.

Appendix B Adverse Event Definitions and Additional Safety Information

B 1 Definition of Adverse Events

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

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

B 2 Definitions of Serious Adverse Event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

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

B 3 Life Threatening

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

B 4 Hospitalization

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

B 5 Important Medical Event or Medical Treatment

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

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

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

B 6 Intensity Rating Scale:

1 mild (awareness of sign or symptom, but easily tolerated)

2 moderate (discomfort sufficient to cause interference with normal activities)

3 severe (incapacitating, with inability to perform normal activities)

B 7 A Guide to Interpreting the Causality Question

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

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

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

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

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

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

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

B 8 Medication Error

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

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

Medication error includes situations where an error.

- occurred
- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were recognize that could have led to an error

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

- Drug name confusion
- Dispensing error e.g. medication prepared incorrectly, even if it was not actually given to the participant

- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g. tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g. kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to participant (excluding IVRS/IWRS errors)

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

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

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

Appendix C National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis

Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson FN Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report -- Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006; 117:391-7.

National Institute of Allergy and Infectious Diseases (NIAID) and Food Allergy and Anaphylaxis Network (FAAN) define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to > 95% of all cases of anaphylaxis (for all 3 categories).

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

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

D 1 Introduction

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

During the course of the study, the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a subject meets potential Hy's Law criteria at any point during the study.

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

The investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible potential Hy's Law events.

The investigator participates, together with MedImmune clinical project representatives, in review and assessment of cases meeting potential Hy's Law criteria to agree whether Hy's Law criteria are met. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury (DILI) caused by the investigational product.

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

D 2 Definitions

D 2.1 Potential Hy's Law

AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN at any point during the study following the start of investigational product irrespective of an increase in alkaline phosphatase (ALP).

D 2.2 Hy's Law

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

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

D 3 Identification of Potential Hy's Law Cases

In order to identify cases of potential Hy's Law, it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

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

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

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

- Notify the sponsor study representative
- Request a repeat of the test (new blood draw) by the central laboratory without delay
- Complete the appropriate unscheduled laboratory case report form (CRF) module(s) with the original local laboratory test result

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

- Determine whether the subject meets potential Hy's Law criteria (see Section D 2) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

D 4 Follow-up

D 4.1 Potential Hy's Law Criteria Not Met

If the subject does not meet potential Hy's Law criteria the investigator will:

- Inform the study representative that the subject has not met potential Hy's Law criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the study protocol.

D 4.2 Potential Hy's Law Criteria Met

If the subject does meet potential Hy's Law criteria the investigator will:

- Notify the sponsor study representative who will then inform the study team
- Within 1 day of potential Hy's Law criteria being met (Appendix D 6), the investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to clinical study protocol process for SAE reporting

The medical monitor contacts the investigator, to provide guidance, discuss and agree on an approach for the study subjects' follow-up (including any further laboratory testing) and the continuous review of data.

- Subsequent to this contact the investigator will:
  - Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Complete follow-up SAE Form as required.
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the medical monitor. This includes deciding which the tests available in the Hy's Law lab kit should be used.
  - Complete the relevant CRF Modules as information becomes available

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

The instructions in this section should be followed for all cases where potential Hy's Law criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the medical monitor will contact the investigator in order to review available data and agree on whether there is an alternative explanation for meeting potential Hy's Law criteria other than DILI caused by the investigational product, to ensure timely analysis and reporting to health authorities per local requirements from the date potential Hy's Law criteria were met. The medical monitor and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

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

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

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

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

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

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

- Provide any further update to the previously submitted SAE of Potential Hy's Law (report term now 'Hy's Law case'), ensuring causality assessment are related to the

investigational product and seriousness criteria is medically important, according to the clinical study protocol process for SAE reporting

! Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether Hy's Law criteria are still met. Update the previously submitted potential Hy's Law SAE report following clinical study protocol process for SAE reporting, according to the outcome of the review and amend the reported term if an alternative explanation for the liver biochemistry elevations is determined

D 6 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a subject meets potential Hy's Law criteria on study treatment and has already met potential Hy's Law criteria at a previous on study treatment visit.

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

The investigator should determine the cause for the previous occurrence of potential Hy's Law criteria being met and answer the following question:

! Was the alternative cause for the previous occurrence of potential Hy's Law criteria being met found to be the disease under study eg, chronic or progressing malignant disease, severe infection, or liver disease.

If **No**: follow the process described in Section D 4.2, for reporting potential Hy's Law as an SAE.

If **Yes**: Determine if there has been a significant change in the subject's condition compared with when potential Hy's Law criteria were previously met:

! If there is no significant change no action is required
! If there is a significant change follow the process described in Section D 4.2, for reporting potential Hy's Law as an SAE

A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the medical monitor if there is any uncertainty.

D 7 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory when using a central laboratory. For studies using a local laboratory, the list may be modified based on clinical judgement. If required, for additional assistance on which tests could be used to evaluate other potential causes of liver dysfunction, consult with the Hepatic Safety Knowledge Group. Any test results need to be recorded.

Hy's Law lab kit for central laboratories

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

*HCV RNA is only tested when IgG anti-HCV is positive or inconclusive

REFERENCES

Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'

Appendix E Genetic Research

Rationale and Objectives

MedImmune intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. Genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications.

In addition, collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical studies and, possibly, to genetically guided treatment strategies.

Genetic Research Plan and Procedures

Selection of genetic research population

Study selection record

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

Inclusion criteria

For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**:

! Provide informed consent for the genetic sampling and analyses.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

Discontinuation of subjects from this genetic research

Specific reasons for discontinuing a subject from this genetic research are:

Withdrawal of consent for genetic research: Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 4.1.7 of the protocol.

Collection of samples for genetic research

The blood sample for genetic research will be obtained from the subjects at Visit 3 (Day 1). Only one sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years, from the date of last subject last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional second code will be assigned to the blood either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable by the second, unique number only. This number is used to identify the sample and corresponding data at the MedImmune genetics laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (MedImmune employee or designated organizations working with the DNA).

The link between the subject enrolment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at MedImmune or designated organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 7 of the protocol.

Informed consent

The genetic component of this study is optional, and the subject may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the subject must sign and date the consent form for the main study and on the same consent form indicate their agreement to be included in the genetic component of the study. A copy of the signed and dated consent form must be given to the subject and the original filed at the study center. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely discontinue from the genetic aspect of the study at any time.

Subject data protection

MedImmune will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, a MedImmune Physician or an investigator might know a subject's identity and also have access to his or her genetic data. Also, Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

Data management

Any genotype data generated in this study will be stored at a secure system at MedImmune and/or designated organizations to analyze the samples.

The results from this genetic research may be reported in a separate report from the CSR or published in scientific journals.

MedImmune and its designated organizations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as Hospitals, Academic Organization or Health Insurance Companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health related research purposes. Researchers may see summary results, but they will not be able to see individual subject data or any personal identifiers.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical Methods and Determination of Sample Size

The number of subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

Appendix F Alcohol use disorder identification test (AUDIT)

Alcohol Use Disorders Identification Test - Self Report Version - (AUDIT)					
PATIENT: Because alcohol use can affect your health and can interfere with certain medications and treatments, it is important that we ask some questions about your use of alcohol. Your answers will remain confidential so please be honest. **Place an X in 1 box that best describes your answer to each question.**					
Questions	**0**	**1**	**2**	**3**	**4**
1 How often do you have a drink containing alcohol?	☐ Never	☐ Monthly or less	☐ 2-4 times a month	☐ 2-3 times a week	☐ 4 or more times a week
2 How many drinks containing alcohol do you have on a typical day when you are drinking?	☐ 1 or 2	☐ 3 or 4	☐ 5 or 6	☐ 7 to 9	☐ 10 or more
3 How often do you have six or more drinks on one occasion?	☐ Never	☐ Less than monthly	☐ Monthly	☐ Weekly	☐ Daily or almost daily
4 How often during the last year have you found that you were not able to stop drinking once you had started?	☐ Never	☐ Less than monthly	☐ Monthly	☐ Weekly	☐ Daily or almost daily
5 How often during the last year have you failed to do what was normally expected of you because of drinking?	☐ Never	☐ Less than monthly	☐ Monthly	☐ Weekly	☐ Daily or almost daily
6 How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	☐ Never	☐ Less than monthly	☐ Monthly	☐ Weekly	☐ Daily or almost daily
7 How often during the last year have you had a feeling of guilt or remorse after drinking?	☐ Never	☐ Less than monthly	☐ Monthly	☐ Weekly	☐ Daily or almost daily
8 How often during the last year have you been unable to remember what happened the night before because of your drinking?	☐ Never	☐ Less than monthly	☐ Monthly	☐ Weekly	☐ Daily or almost daily

Alcohol Use Disorders Identification Test - Self Report Version - (AUDIT)					
PATIENT: Because alcohol use can affect your health and can interfere with certain medications and treatments, it is important that we ask some questions about your use of alcohol. Your answers will remain confidential so please be honest. **Place an X in 1 box that best describes your answer to each question.**					
Questions	**0**	**1**	**2**	**3**	**4**
9 Have you or someone else been injured because of your drinking?	☐		☐		☐
	No		Yes, but not in the last year		Yes, during the last year
10 Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?	☐		☐		☐
	No		Yes, but not in the last year		Yes, during the last year
				Total	_____

Appendix G Alcohol use disorder identification test (AUDIT) - Scoring instructions

Scoring the AUDIT questionnaire

Scores for each question range from 0 to 4, with the first response for each question (eg, never) scoring 0, the second (eg, less than monthly) scoring 1, the third (eg, monthly) scoring 2, the fourth (eg, weekly) scoring 3, and the last response (eg, daily or almost daily) scoring 4. For questions 9 and 10, which only have 3 responses, the scoring is 0, 2, and 4 (from left to right). A score of 8 or more is associated with harmful or hazardous drinking, a score of 13 or more in women, and 15 or more in men, is likely to indicate alcohol dependence.

Definition of a standard drink

In the AUDIT, questions 2 and 3 it is assumed that a standard drink equivalent is 10 grams of alcohol. The alcohol content of a drink depends on the strength of the beverage and the volume of the container.

The investigator should adjust the number of drinks in the response categories for these questions in order to fit the most common drink sizes and alcohol strength in their country.

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Document Title:	D5671C00002 Clinical Study Protocol Amendment 6	
Document ID:	Doc ID-004250975	
Version Label:	2.0 CURRENT LATEST APPROVED	
Server Date (dd-MMM-yyyy HH:mm 'UTC'Z)	**Signed by**	**Meaning of Signature**
02-Dec-2020 16:03 UTC	PPD	Management Approval
02-Dec-2020 16:17 UTC	PPD	Content Approval
03-Dec-2020 13:04 UTC	PPD	Content Approval
03-Dec-2020 04:56 UTC	PPD PPD	Content Approval
02-Dec-2020 20:15 UTC	PPD	Qualified Person Approval

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