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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)

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AB	Abdominal
ABPM	Ambulatory blood pressure monitoring
AC	Activity
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
ATC	Anatomical therapeutic chemical
AUC	Plasma area under the concentration-time curve
AUDIT	Alcohol use disorder identification test
BARD	BMI, Ratio, Diabetes Score
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
CAP	Percentage-controlled attenuation parameter
CI	Confidence interval
CK18	Cytokeratin 18
CLDQ-NASH	Chronic Liver Disease Questionnaire for non-alcoholic steatohepatitis
CM	Concomitant medication
Cmax	Maximum observed plasma drug concentration
Covance BM	Covance biometric
CS	Compound symmetry covariance structures
CSR	Clinical study report
D	Day
dECG	Digital electrocardiogram
E-code	Subject identification number
eCRF	Electronic case report form
ELF™	Enhanced liver fibrosis score
EM	Emotion
EOS	End of study

Abbreviation or special term	Explanation
EOT	End of treatment
FA	Fatigue
FIB-4	Fibrosis-4 score
FLI	Fatty liver index
FSH	Follicle-stimulating hormone
FUP	Follow-up
GGT	Gamma glutamyl transferase
GLP-1	Glucagon-like peptide-1
HbA1c	Haemoglobin A1c
HDLc	High density lipoprotein cholesterol
HFF	Hepatic fat fraction
HIV	Human immunodeficiency virus
HOMA-IR	Homeostatic model assessment of insulin resistance
HR	Heart rate
IA	Interim analysis
IC	Informed consent
IDRP	Integrated Data Review Plan
IP	Investigational product
IPD	Important protocol deviation
ITT	Intention to treat
IU	International units
LDLc	Low density lipoprotein cholesterol
LOCF	Last observation carried forward
LSM	Liver stiffness measurement
LSmeans	Least-square means
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
MRI-PDFF	Magnetic resonance imaging-proton density fat fraction
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NHP	Non-compliance handling plan
NIS4	Non-invasive diagnostic score 4
NFS	NAFLD fibrosis score
P4NP7S	Internal epitope in the 7S domain of type IV collagen
PCS	Physical component summary

Abbreviation or special term	Explanation
PD	Protocol deviation
PK	Pharmacokinetic
PP	Per protocol
PPAR-γ	Peroxisome proliferator-activated receptor gamma
PR	PR wave
PRO	Patient reported outcome
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
PT	Preferred term
QRS	QRS wave
QT	QT wave
QTcB	Corrected QT Interval using Bazett's Formula
QTcF	Corrected QT Interval using Fridericia's Formula
REML	Restricted maximum likelihood
RPP	Rate pressure product
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SDTM	Study data tabulation model
SE	Standard error
SF-36	Short-Form-36
SGLT-2	Sodium-glucose co-transporter 2
SI	International system of units
SOC	System organ class
SP (POW)	Power spatial covariance structures
SY	Systemic
T2DM	Type 2 diabetes mellitus
TBL	Total bilirubin
TEAE	Treatment emergent adverse event
Tmax	Time to maximum observed plasma drug concentration
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
UN	Unstructured covariance structures

Abbreviation or special term	Explanation
UNSCH	Unscheduled
V	Visit
WHO	World Health Organization
WHO-DD	WHO Drug Dictionary
WO	Worry
β-HB	β-hydroxybutyrate

AMENDMENT HISTORY

Version number	Date	Brief description of change
V1.0	22/10/2019	N/A
V2.0	05/08/2020	Amendment due to protocol amendment; changes in statistical modelling for exploratory endpoints; additional Safety tables; added the ad-hoc safety review; added tables at IA
V3.0	28/09/2020	AVISIT derivation: added range for CRF visits
V4.0	11/11/2020	Added for HFF only: descriptive statistics by T2DM, p-values for change from baseline within each group and comparison between all active patients versus placebo
V5.0	01/06/2021	Deleted the Disease related medical history page because not recorded correctly in the CRF; added COVID tables and other minor changes

1 STUDY DETAILS

1.1 Study objectives

1.1.1 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.

1.1.2 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 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

1.1.3 Exploratory objectives and associated endpoints

CCI [redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Table 3 Exploratory objectives and associated endpoints

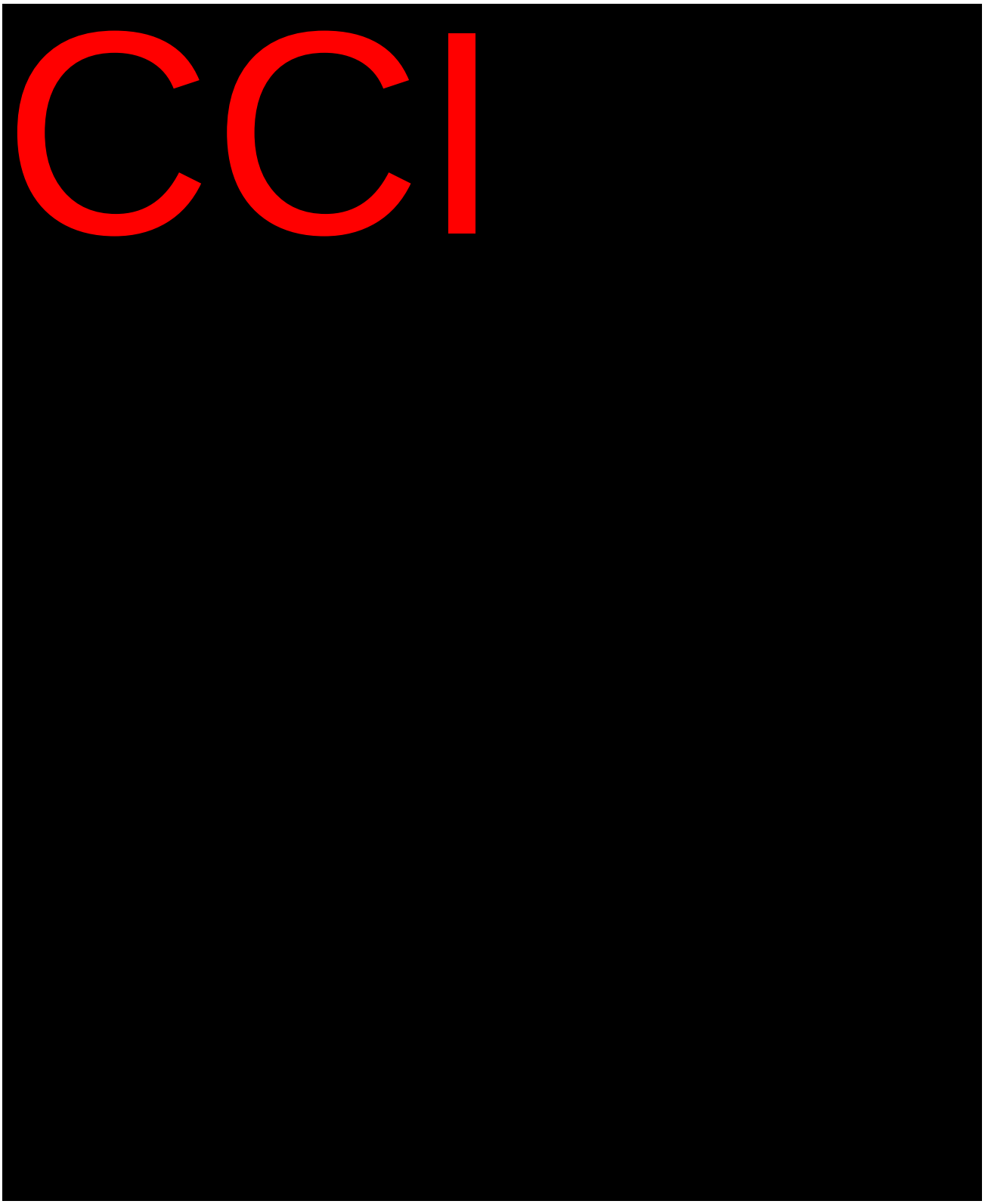
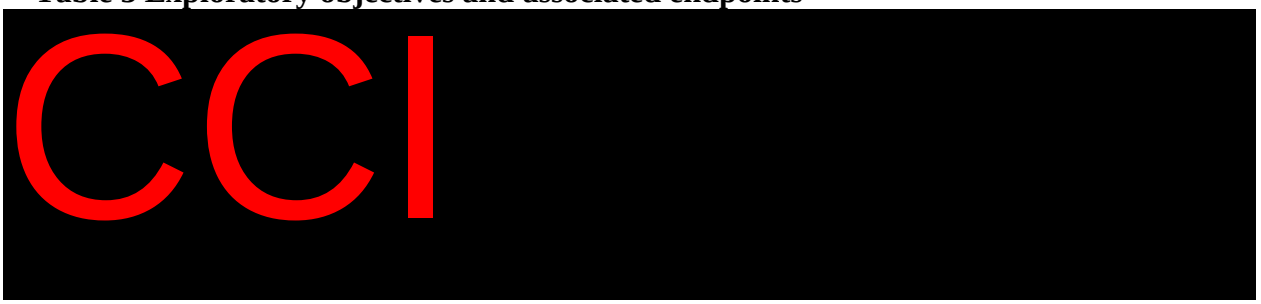


Table 3 Exploratory objectives and associated endpoints



1.2 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 have biopsy-confirmed NAFLD/NASH with liver fibrosis stages F1, F2 or F3. Approximately 72 subjects are randomized across multiple study sites.

Subjects are 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).

The table below shows all procedures to be conducted at the screening visit.

Table 4 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	

Table 4 Screening schedule of procedures

Study Period	Screening	
Visit Number	**V1**	**V2[f]**
Procedure/Study Day	**Day -28 to -11**	**Day -10 ± 3 days**
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	
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 = haemoglobin A1c; HIV = human immunodeficiency virus; 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.

The tables below show all procedures to be conducted during the treatment period for MEDI0382/Placebo 300 µg and MEDI0382/Placebo 600 µg, respectively.

Table 5 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

Table 5 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**
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)												
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

Table 5 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
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
Serum markers of liver fibrosis[m]	x							x				x
NIS4	x							x				x
Amino acids panel	x[n]							x				x

Table 5 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
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

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 = haemoglobin

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.

[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 ± 5 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 6 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						

Table 6 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
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	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

Table 6 MEDI0382/matched placebo 600 µg treatment period schedule of procedures

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	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
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
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

Table 6 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
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
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

Table 6 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**
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

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 = haemoglobin 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 hypoglycaemia (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.

[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 ± 5 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 MRIPDFF) 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:

- 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.

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.

The table below shows all procedures to be conducted during the follow-up period.

Table 7 Schedule of follow-up procedures

Study Period	**Follow-up Period/Early Discontinuation**
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

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 = haemoglobin 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 = .

[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 5 or Table 6 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.

Additional details on study design are provided in the study protocol.

1.3 Number of subjects

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 assume a 25% dropout rate, 24 subjects per group 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.

2 ANALYSIS SETS

2.1 Definition of analysis sets

In Table 8 here below are reported all the analyses sets.

Table 8 Definition of analysis sets

Population	Description
All enrolled subject	All enrolled subjects include those who have signed the informed consent form. All enrolled subject population will be analysed according to the randomized treatment group.

Table 8 Definition of analysis sets

Population	Description
Intent-to-treat (ITT) population	The ITT population includes all enrolled subjects who are randomized. ITT population will be analysed according to the randomized treatment group. The analyses include the post IP-discontinuation data for those subjects who discontinue from study treatments but are still followed up for their scheduled visits.
As-treated population	The as-treated population includes all enrolled subjects who are randomized and have received at least one dose of study IP. As-treated population will be analysed according to the actual treatment received. To determine the actual treatment for a subject, the general rule is that if a subject receives placebo as well as active treatments then this subject's actual treatment will be chosen from the active treatments only. 1. If only placebo kits are delivered to the subject, then the actual arm will be set to placebo 2. If only MEDI0382 kits are delivered to the subject, then ➢ if the max dose is lower or equal to 300 µg, the actual arm will be set to MEDI0382 300 µg ➢ if the max dose is greater to 300 µg, the actual arm will be set to MEDI0382 600 µg 3. If the subject was provided both with MEDI0382 and placebo kits, then: ➢ If the subject is randomized to MEDI0382 300 or MEDI0382 600 groups, the actual arm is assigned as described in point 2 above ➢ If the subject is randomized to placebo group and received MEDI0382 kits in more than one delivery visit, the actual arm will be evaluated case by case, looking to the reported doses and, in case needed, raising queries to the involved personnel. ➢ If the subject is randomized to placebo group and received MEDI0382 kits in only one delivery visit, then • if the first dose following or on the wrong kit delivery date is lower or equal to 300 µg, the actual arm will be set to MEDI0382 300 µg • if the first dose following or on the wrong kit delivery date is greater to 300 µg, the actual arm will be set to MEDI0382 600 µg The analyses include the post IP-discontinuation data for those subjects who discontinue from study treatments but are still followed up for their scheduled visits.
Per-protocol (PP) population	The PP population includes all enrolled subjects who are randomized and have received at least one dose of study IP except for subjects who have discontinued the study IP and those with relevant important protocol deviations(IPD). Relevant IPD are those that have the potential to affect the result of the primary efficacy results and are reported section 2.2. List of subjects to be excluded from the PP population will be also discussed and agreed with the blinded study team in a dedicated meeting prior to database lock. PP population is analysed according to the randomized treatment group.

2.2 Violations and deviations

The list of important protocol deviations (IPDs) is provided in the AstraZeneca non-compliance handling plan (NHP). Relevant IPD that lead to subject exclusion form the PP population are a subset of all IPD. More specifically they are:

IPD as per NHP v3.0		Relevant IPD
1 Those who entered the study even though they did not satisfy the entry criteria (ICH3) - Inclusion criteria		
1.01	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	Y
1.02	Subjects aged ≥ 18 years at the time of consent	Y
1.03	BMI ≥ 30 kg/m2 at screening	Y
1.04	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)	Y
1.05	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	Y
1.06	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)	Y
1.07	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	Y
2 Those who entered the study even though they did not satisfy the entry criteria (ICH3) - Exclusion criteria		
2.01	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	Y
2.02	Liver disease of other etiologies (eg, alcoholic steatohepatitis; drug-induced, viral, or autoimmune hepatitis; primary biliary cirrhosis; primary sclerosing cholangitis; hemochromatosis; alpha 1 antitrypsin deficiency; Wilson's disease) including positive results for hepatitis B surface antigen (HBsAg) or hepatitis C antibody tests (anti-HCV)	Y
2.03	History of cirrhosis and/or hepatic decompensation, including ascites, hepatic encephalopathy or variceal bleeding	Y
2.04	Prior or planned liver transplantation	Y
2.05	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	Y
2.06	Evidence of alcohol dependence as assessed by the Alcohol Use Disorder Identification Test (AUDIT) questionnaire at screening	Y
2.07	A history of type 1 diabetes mellitus (T1DM), a history of diabetic ketoacidosis or current use of insulin-based therapies	Y

2.08	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	Y
2.09	Physician-diagnosed diabetic subjects with clinically significant gastroparesis (as judged by the investigator) or those treated for gastroparesis within 6 months prior to screening	Y
2.10	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 (eg, orlistat, bupropion/naltrexone, phentermine-topiramate, phentermine, lorcaserin), as well as those drugs used off-label	Y
2.11	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	Y
2.12	Severe congestive heart failure (New York Heart Association Class IV)	Y
2.13	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	Y
2.14	History of substance dependence likely to impact subject safety or compliance with study procedures, or positive screen for drugs of abuse at screening (CSP 1.0. 2.0 & 3.0)	Y
2.15	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	Y
2.16	Recent (within 3 months of baseline biopsy) use of therapies associated with development of NAFLD (eg, systemic corticosteroids, methotrexate, tamoxifen, amiodarone, or long-term use of tetracyclines)	Y
2.17	Recent (within 3 months of baseline biopsy) use of obeticholic acid or other therapy under investigation for NASH	Y
2.18	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	Y
2.19	Recent (within 3 months of baseline biopsy) use of GLP-1 receptor agonist or GLP-1 receptor agonist containing therapies	Y
2.20	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	Y
2.21	Concurrent participation in another interventional study of any kind or repeat randomization in this study	Y
2.22	Severe allergy/hypersensitivity to any of the proposed study treatments or excipients	Y
2.23	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	Y
2.24	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	Y

2.25	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 m2 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/mm3. (g) Any other clinically significant abnormalities in clinical chemistry, hematology, or urinalysis results as judged by the investigator	Y
2.26	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	Y
2.27	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)	Y
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	Y
2.29	Any positive results for human immunodeficiency virus (HIV) infection	Y
2.30	Any AstraZeneca, MedImmune, or study site employee, or close relatives of any of the aforementioned employees	Y
2.31	Females who are pregnant or lactating	Y
2.32	History of substance dependence or a positive screen for drugs of abuse, likely to impact subject safety or compliance with study procedures, or positive screen for drugs of abuse at screening, at the discretion of the Investigator (CSP 4.0 and onward)	Y

3 Those who developed discontinuation/ withdrawal criteria during the study but were not withdrawn from treatment (ICH3)

3.01	An adverse event that, in the opinion of the Investigator or AstraZeneca, warrants discontinuation from further dosing	Y
3.02	Patient noncompliance that, in the opinion of the Investigator or sponsor, warrants withdrawal (e.g. refusal to adhere to scheduled visits)	Y
3.03	Pregnancy in a female subject.	Y
3.04	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	Y
3.05	Acute viral hepatitis	Y
3.06	Symptoms or signs of cirrhosis and/or hepatic decompensation (e.g., ascites, variceal bleeding, hepatic encephalopathy).	Y
3.07	Acute pancreatitis.	Y

4 Those who developed discontinuation/ withdrawal criteria during the study but were not withdrawn from Study (ICH3)

4.01	Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be initiated on treatment, and must be withdrawn from the study	Y

5 Subject received the wrong treatment or incorrect dose. (ICH3)

5.08	Subject missed IP dose for ≥7 contiguous days or less than 80% compliance overall. Note: the first 7 days of dosing (D1-D7) are mandatory and if any single doses are missed during this period then it would constitute an IPD. If a subject misses a dose due to an AE is not considered an IPD, in this case it would be a non important protocol deviation. It would also be considered NIPD if a dose was missed due to an AE during the first 7 days of dosing.	Y
5.10	Subjects with 5.01 - 5.05 for more than 2 weeks	Y

6 Subject received prohibited medications (ICH3)

6.02	Subject received prohibited procedures, see exclusion criteria: liver transplantation.	Y
6.03	Subjects with 6.01 for more than 2 weeks	Y

3 BASELINE, EFFICACY AND SAFETY EVALUATION

3.1 General principles

3.1.1 Handling of missing data

Missing data are not replaced unless otherwise specified for statistical modelling. Only date of first and last dose of IP, AE start and end date and concomitant medications (CMs) end date are imputed. Imputation rules are reported below.

3.1.1.1 Imputation of date of first dose of IP

Date and time of first dose of IP are mandatory eCRF fields. No Imputations are expected. In the rare cases of missing date, the date of first dose of IP will be imputed if all the following criteria are met:

- There is a completely missing or partial missing date for the first dose of IP, and
- There is at least one kit for which the amount of drug dispensed does not equal the amount of drug returned, and
- The kits for which the amount of drug dispensed does not equal the amount of drug returned have complete non-missing dispensed date

If that is the case, the date of first dose of IP is imputed with the earliest dispensed date from kits for which amount of drug dispensed does not equal the amount of drug returned. Completely missing time and time where only hour is missing is imputed to 00:00. If only minutes are missing, then it will be imputed to HH:00.

3.1.1.2 Imputation of date of last dose of IP

Last dose date and time are mandatory eCRF fields. No Imputations are expected. In the rare cases of missing date, the last dose date of study drug is imputed if all the following criteria are met:

- There is a completely missing or partial missing date for the last dose of study drug, and
- There is at least one kit for which the amount of drug dispensed does not equal the amount of drug returned, and
- The kits for which the amount of drug dispensed does not equal the amount of drug returned have complete non-missing returned date.

If that is the case, last dose date of study drug is imputed with the latest returned date from kits for which amount of drug dispensed does not equal the amount of drug returned. Missing time is not replaced.

3.1.1.3 Imputation of AE end date

Completely missing AE end dates are not imputed. Partial missing AE end dates are imputed as below:

- If the AE is ongoing, the end date is stated to missing.
- If the AE is not ongoing, and if only the day is missing: Assume the last day of the collected month.
- If the AE is not ongoing, and both, the day and the month are missing: Assume 31-DEC of the collected year.

After applying these rules, if the imputed AE end date is after the end of study date, the AE is set to ongoing and the AE end date to missing.

3.1.1.4 Imputation of AE start date

Before to proceed with the AE start date imputation, the first dose of IP and the AE end date are imputed as described in the previous section.

Only partial AE start dates are imputed; Dates which are completely missing are not imputed. Partial dates are imputed as described below:

If the day is missing and the month and year are different from the month and year of the first dose of IP, assume 01-MMM-YYYY. If the month and year are the same as the first dose of IP month and year and the end date is on or after (including ongoing / missing) the first dose of IP, then assume the date of the first dose of IP. If the month and year are the same as the first dose of IP month and year and the end date is prior to the first dose of IP, then assume the end date.

If the month is missing and the year is different from the year of first dose of IP, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of IP year and the end date is on or after (including ongoing / missing) the first dose of IP, then assume the date of the first dose of IP. If the year is the same as the first dose of IP and the end date is prior to the first dose of IP, then assume the end date.

After applying these rules, if the imputed AE start date is after a complete AE end date then assume the same date as the complete AE end date; if the end date is missing and the imputed AE start date is after the end of study date then assume the same date as the study end date.

3.1.1.5 Imputation of concomitant medication end date

Completely missing concomitant medication end dates are not imputed. Partial missing concomitant medication end dates are imputed as below:

- If the CM is ongoing, the end date is set to missing.
- If the CM is not ongoing, and if only the day is missing: Assume the last day of the of the collected month.
- If the CM is not ongoing, and both, the day and the month are missing: Assume 31-DEC of the collected year.

After applying these rules, if the imputed CM is after the end of study date, the CM is set to ongoing and the CM end date to missing.

3.1.1.6 Imputation of concomitant medication start date

Both, completely missing and partially missing concomitant medication start dates are not imputed.

3.1.2 Analysis visit windows

For the purpose of the statistical analysis primary, secondary and exploratory endpoints, except the adverse event, are allocated to the analysis visit as reported in the tables below. The allocation to visit windows is performed after the imputation of date of first and last doses of IP as in section 3.1.1. Measurements with missing or partially missing dates cannot be imputed to any analysis visit.

Table 9 Analysis visit windows

Analysis visit (AVISIT)	Scheduled visit day	Visit Window (Days)
Pre-treatment	From -28 to 1[l]	<=1[a]
Day 1	1	1[b]
Week 2	8	8 - 9
Week 4	22	20 - 24
Week 6	36	34 - 38
Week 8	50	48 - 52[c]
Week 8	50	48 - 52[d]
Week 8 (D51)	51	If in 48 - 53 then CRF Week 8 (D51)[e]
Week 8 (D52)	52	If in 48 - 54 then CRF Week 8 (D52)[e]
Week 10	64	62 - 66[c]

Table 9 Analysis visit windows

Analysis visit (AVISIT)	Scheduled visit day	Visit Window (Days)
Week 10	64	62 - 66[f]
Week 10 (D65)	65	If in 62 - 67 then CRF Week 10 (D65)[e]
Week 10 (D66)	66	If in 62 - 68 then CRF Week 10 (D66)[e]
Week 12[h]	78	76 - 80[c]
Week 12 [h]	78	76 - 80[g]
Week 12 (D79)	79	If in 76 - 81 then CRF Week 12 (D79)[e]
Week 12 (D80)	80	If in 76 - 82 then CRF Week 12 (D80)[e]
Week 14	92	88 - 96
Week 16	106	102 - 110
Week 18	120	116 - 124
Week 19[i]	133	129 - 137
Week 23	161	155 - 166

[a] Includes all measurements collected before or on day 1 prior to first dose of IP. If the measurement is collected on day 1 but it cannot be determined if it was done before or after the first dose of IP (due to missing time and/or planned time point), then it will be considered as collected before the first dose of IP. For height, weight, BMI, waist and hip circumference and lipidomics, if the measurement is collected on day 1 is always considered collected before the first dose of IP.

[b] Includes all measurements collected at day 1 on or after the first dose of IP.

[c] Only for subjects in MEDI0382 /placebo 300 µg treatment group.

[d] Only for subjects in MEDI0382 /placebo 600 µg treatment group. Excluding Week 8 (D51) and Week 8 (D52).

[e] Only for subjects in MEDI0382 /placebo 600 µg treatment group.

[f] Only for subjects in MEDI0382 /placebo 600 µg treatment group. Excluding Week 10 (D65) and Week 10 (D66)

[g] Only for subjects in MEDI0382 /placebo 600 µg treatment group. Excluding Week 12 (D79) and Week 12 (D80)

[h] MRI windows is 76 – 85

[i] MRI windows is 129 – 147

[l] MRI scheduled visit day is from - 60 days to 1

After having assigned the visit windows as described above, if there are measurements which have not yet the analysis visit assigned, they are labelled as reported in the table below.

Table 10 Analysis visit windows for unscheduled visits

Analysis visit (AVISIT)	Visit Window (Days)
UNSCH Early Discontinuation	1 day to 9 days (included) after last dose of IP [a]
UNSCH Follow-up	23 days to 33 days (included) after last dose of IP[b]
UNSCH 1.x	2 - 7
UNSCH 2.x	10 - 19
UNSCH 4.x	25 - 33
UNSCH 6.x	39 - 47
UNSCH 8.x	53 - 61
UNSCH 10.x	67 – 75
UNSCH 12.x	81 – 87 [d]
UNSCH 14.x	97 - 101
UNSCH 16.x	111 - 115
UNSCH 18.x	125 – 128
UNSCH 19.x	138 – 154[f]
UNSCH 23.x	>166

[a] Unscheduled early discontinuation visit (UNSCH Early Discontinuation) is used only for subjects who discontinue the study IP before visit at week 19. If a measurement falls within the UNSCH Early Discontinuation then cannot be assigned to any other unscheduled analysis visit.

[b] Unscheduled follow up visit (UNSCH Follow-up) is used only for subjects who discontinue the study before week 19. If a measurement falls within the UNSCH Follow-up analysis visit then cannot be assigned to any other unscheduled analysis visit.

[d] MRI windows is 86 – 87

[f] MRI windows is 141 – 154

The unscheduled visits will be numbered sequentially with an increment of 0.1. For example, if two measurements are done in the unscheduled visits that occur between visit Week 4 and visit Week 6, then these unscheduled visits will be numbered UNSCH 4.1 and UNSCH 4.2 in the order they occurred. The unscheduled visits are not summarized in tables but only presented in listing.

For the purpose of the statistical analysis:

- the baseline value used for statistical analyses is the last available value among those in the pre-treatment visit window. If several measurements are collected during the selected day, the average (for numeric values)/worst (for categorical values) of the measurements is taken. If there are several categorical values corresponding to the worst case, then the last measurement registered in CRF will be taken.
- all the other post baseline visit values, except vital signs:

- If more than one measurement falls in the same visit window but in different days, the nearest to the scheduled visit day is taken. If several measurements are collected within the same distance from the scheduled study day, the data of the latest visit after the scheduled study day within that window is used.

- If several measurements are collected during the selected day, the average (for numeric values)/worst (for categorical values) of the measurements is taken. If there are several categorical values corresponding to the worst case, then the last measurement registered in CRF will be taken.

- post-baseline visit values for vital signs:

  - all eCRF planned timepoints within the same day are kept separately for the statistical analysis. If more than one measurement falls in the same visit window but in different days, the nearest to the scheduled visit day is taken. If several measurements are collected within the same distance from the scheduled study day, the data of the latest visit after the scheduled study day within that window is used. Except for Week 23, if the selected day has no timepoints, it cannot be considered for the statistical analysis and the subsequent nearest day needs to be considered. For Week 23, if several measurements are collected during the selected day, the average of the measurements is taken.

3.1.3 Study phase windows

For the purpose of the statistical analysis primary, secondary and exploratory endpoints are allocated to the study phase in which they are collected as reported below. The allocation to the study phases (Table 11) is performed after the imputation of date of first and last doses of IP as in section 3.1.1. The allocation of the AEs to the study phases is performed after the imputation of AE start and AE end dates as reported in section 3.1.1.

Table 11 Study phases

Study phase	Phase Window for Analysis (Days)
Pre-treatment	before first dose of study IP (day <1[a])
On-treatment	from day 1[b] to day of last dose of IP (included)
Follow-up	> day of last dose of IP (not included)

[a] Includes all measurements collected before first dose of IP. If the measurement is collected on the day of first dose of IP but the time of collection (or the planned timepoint) cannot determine if the measurement was before or after first dose of IP, then it will be considered as collected before first dose of IP.

[b] Includes all measurements collected on the day of first dose of IP, at the time of IP intake and after.

3.2 Baseline assessments and other subject-specific characteristics

Demographic and subject characteristics, medical history and nicotine and alcohol use are collected pre-treatment as per section 1.2.

3.2.1 Demographic and subject characteristics

Demographic and subject characteristics include age, age group (<50; >=50 -<65; >=65), sex, race, ethnic group, country, height (cm), weight (kg), body mass index (BMI) (kg/m^2), liver fibrosis stage (F1, F2 and F3) and type 2 diabetes mellitus. Age is the age at screening as reported in the eCRF. BMI (kg/m2) is calculated as: weight (kg) divided by the square of height (cm)/100.

Height, weight and BMI are allocated to the concerning analysis visits as per section 3.1.2. Evaluations with missing or partially missing dates cannot be imputed to any analysis visit. Only baseline values are included in the demographic and subject characteristics.

3.2.2 Medical history

Medical history is coded in Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or higher. Diet and exercise history are also collected.

3.2.3 Alcohol use

The AUDIT questionnaire to assess detailed alcohol use habits is completed at screening. Alcohol use (never-current-former) including consumption frequency and unit, is also collected.

3.3 Efficacy and safety variables

The primary objective of the study is the safety of MEDI0382 compared with placebo. Safety endpoints are the adverse events (AE) including serious adverse events (SAEs). Other safety endpoints included in the study are laboratory evaluations, vital signs and dECG.
The secondary objective of the study is the efficacy of MEDI0382 compared with placebo. Secondary efficacy endpoints are:

- Hepatic fat fraction (HFF) as assessed by magnetic resonance imaging-proton density fat fraction (MRI-PDFF);
- Other related imaging parameters as assessed by MRI;
- Circulating markers of hepatic inflammation - ALT, AST and GGT;
- Immunogenicity
- Weight, BMI and waist and hip circumference

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Efficacy and safety endpoints are collected as reported in section 1.2.

3.3.1 Primary safety endpoints

3.3.1.1 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 (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. SAEs will be collected from time of signature of informed consent, throughout the treatment period and including the follow-up period. All non-serious AEs will be recorded from time of first dose of IP, throughout the treatment period and including the follow-up period. Adverse events (AEs) will be coded with MedDRA version 21.0 or later. For any additional details on AE reporting please refer to the study protocol.

The AEs are assigned to the study phases described in section 3.1.3, based on the AE start date and time as follows:

If both the start date and start time of an AE are known, then:

- If the AE start datetime is before the first dose of IP datetime, then the AE is assigned to the pre-treatment phase.
- If the AE start datetime is on or after the first dose of IP datetime through the day of last dose of IP (inclusive), then the AE is assigned to the on-treatment phase,
- If the AE start day is after the day of last dose of IP , then the AE is assigned to the follow-up phase.

If only the start date of an AE is known, and the start time of the AE is unknown, then:

- If the AE start date is before the first dose of IP date, then the AE is assigned to the pre-treatment phase,
- If the AE start date is on or after the first dose of IP date through the day of last dose of IP (inclusive), then the AE is assigned to the on-treatment phase,
- If the AE start date if after the day of last dose of IP , then the AE is assigned to the follow-up phase.

If the start date of an AE is completely missing, the AE is assigned as follow:

- If the AE end date is known and is before the first dose of IP date, then the AE is assigned to the pre-treatment phase,
- If the AE end date is completely missing or if the AE end date is on or after the first dose of IP date no assignation can be done.

The study day of start of the AE is calculated as the start date of the AE - date of the first dose of IP +1 for AE started on or after day 1 and as the start date of the AE - date of the first dose of IP for AE started before day 1. Study day of start of AE is calculated for complete date only.

Imputed dates should not be used. If one of the dates is missing or partially missing, the study day of start of the AE is missing.

All the AE in the on-treatment phase are considered treatment emergent adverse events (TEAEs).

The duration of AE is calculated as the end date of the AE – start date of the AE +1. Duration is calculated for complete date only. Imputed dates should not be used. If one of the dates is missing or partially missing, the duration is missing.

3.3.1.2 Laboratory evaluations

Clinical laboratory safety tests are performed in a central clinical laboratory.

Clinical laboratory safety tests are:

Serum chemistry

- blood urea nitrogen
- creatinine
- total protein
- albumin
- total bilirubin (TBL)
- alkaline phosphatase (ALP)
- alanine aminotransferase (ALT)
- aspartate aminotransferase (AST)
- calcium
- glucose (fasting where required)
- sodium
- potassium
- chloride
- bicarbonate
- phosphorus
- gamma glutamyl transferase (GGT)
- calcitonin
- thyroid stimulation hormone (TSH)
- amylase and lipase

Haematology

- red blood cell count
- haemoglobin
- haematocrit
- absolute white blood cell count
- white blood cell count with percent differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
- platelet count
- mean cell volume
- mean corpuscular haemoglobin concentration
- mean corpuscular haemoglobin

Coagulation parameters

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

Urinalysis

- pH (quantitative)
- specific gravity (quantitative)
- glucose (qualitative)
- blood (qualitative)
- colour (qualitative)
- appearance (qualitative)
- Ketones (qualitative)
- Nitrites (qualitative)
- Protein (qualitative)
- Bilirubin (qualitative)
- Leukocytes (qualitative)
- Urobilinogen (qualitative)

Laboratory data are assigned to the analysis visits and the study phases as described in section 3.1.2 and section 3.1.3 respectively. Evaluations with missing or partially missing dates cannot be imputed to any study phase and analysis visit.

Laboratory test results for haematology, coagulation, clinical chemistry and urinalysis quantitative parameters below the lower limit of quantification (LLOQ) for which the exact value cannot be determined, will be replaced with the LLOQ divided by the squared root of 2.

After the LLOQ replacement, change from baseline to each post-baseline visit for haematology, coagulation, clinical chemistry and urinalysis quantitative parameters is defined as the post-baseline visit value minus the baseline visit value.

After the LLOQ replacement, haematology, coagulation, clinical chemistry and urinalysis quantitative parameters are also classified as normal (if value is within normal reference range), low (if value is below the normal reference range), and high (if value is above the normal reference range) based on the reference range indicator.

After the LLOQ replacement, AST, ALT and total Bilirubin are also classified as below:

AST and ALT:

- <3xULN (or below the LLOQ)
- ≥3 - <5xULN
- ≥5 - < 8xULN
- ≥8xULN

Total bilirubin:

- <1xULN (or below the LLOQ, only for measurements at baseline)
- <2xULN (or below the LLOQ, for all the other non-baseline value)
- ≥2xULN (for all the other non-baseline value)

Occurrences of AST or ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN are reported as SAE (Potential Hy´s law) as described in the study protocol.

3.3.1.3 Vital signs

Vital signs include:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Heart rate (bpm)
- Respiratory rate (breaths per minute)
- Temperature (C)
- Rate pressure product - RPP (mmHg*bpm) – derived variable

The rate pressure product (RPP) is calculated as heart rate * systolic blood pressure. Heart rate and systolic blood pressure should come from the same day, same timepoint.

Vital signs parameters are assigned to the analysis visits as described in section 3.1.2. Evaluations with missing or partially missing dates cannot be imputed to any analysis visit.

Vital signs parameters are also allocated to timepoints within visit based on eCRF timepoints. eCRF timepoints at day 1 are:

- 15 min
- 30 min
- 60 min
- 2 hours

eCRF timepoints at day 8, 22, 36, 50, 64, 78 and 133 are:

- Pre-dose
- 15 min
- 30 min
- 60 min
- 2 hours

eCRF timepoints at day 92, 106, 120 is

- Pre-dose

eCRF timepoints at day 51, 52, 65, 66, 79 and 80 are:

- Pre-Dose mean of supine measurements
- Pre-Dose mean of standing measurements

Change from baseline is defined as the post-baseline visit value minus the baseline value.

Additionally, vital signs values will be classified as normal (if value is within normal reference range), low (if value is below the normal reference range), and high (if value is above the normal reference range) according to the normal reference ranges (Table 12):

Table 12 Vital signs normal reference ranges

Parameter	Normal Reference Ranges
Systolic blood pressure	80 - 130 mmHg
Diastolic blood pressure	50 -80 mmHg
Heart rate	50 - 100 bpm
Respiratory rate	12 - 24 breaths per minute
Temperature	<=37ºC

Systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (bpm) and Rate pressure product - RPP (mmHg*bpm) are also measured using the ambulatory blood pressure monitoring (ABPM) device. The subject wears the monitor/cuff for approximately 24 hours (including overnight at home). The 24-hour window is based on the start of the recording, which will begin with the first valid inflation. Any data collected after the 24-hour window will be excluded from the analysis. 2 inflations per hours are performed during day hours (from 6:00:00 to 22:00:00). 1 inflation per hours is performed during night hours (from 22:00:00 to 6:00:00). ABPM parameters are calculated as below:

Complete ABPM systolic blood pressure, diastolic blood pressure and heart rate are derived as the arithmetic means of the single measurements in the 24h.

Day ABPM systolic blood pressure, diastolic blood pressure and heart rate are derived as the arithmetic means of the single measurements considering only the day hours. Day hours from 6:00:00 to 22:00:00 are included.

Night ABPM systolic blood pressure, diastolic blood pressure and heart rate are derived as the arithmetic means of the single measurements considering only the night hours. Night hours from 22:00:01 to 05:59:59 are included.

Single measurements with missing or zero numeric values or out of acceptable range values (as per table below) or for which the visit status is set to not done should not be used in the calculation.

Table 13 ABPM acceptable ranges

Parameter	ABPM acceptable ranges
Systolic blood pressure	10 - 250 mmHg
Diastolic blood pressure	5 - 200 mmHg
Heart rate	1 – 200 bpm

The ABPM rate pressure product (RPP) is calculated as heart rate * systolic blood pressure. Heart rate and systolic blood pressure should come from the same day, same timepoint (complete-night and day).

Additionally, the entire visit, for all the parameters, should be considered of poor quality and so discarded from the analysis if any of the following is true:

- there are less than 18 valid hours out of the total 24 hours (a valid hour is when there is at least one valid measurement during that hour) for at least one of the parameters.
- there are more than 3 consecutive missing hours out of the 24 total hours (missing hour is when there are not valid measurements during that hour) for at least one of the parameters.
- there are less than the 70% of successful measurements out of the total measurement recorded for at least one of the parameters.

ABPM parameters are then assigned to the analysis visits as described in section 3.1.2. Evaluations with missing or partially missing dates cannot be imputed to any analysis visit.

3.3.1.4 dECG

dECG evaluation includes:

- PR interval (msec)
- QRS duration (msec)
- QT interval (msec)
- Heart rate (beats/min)
- QTcB interval (msec)
- QTcF interval (msec)
- Overall evaluation (normal, abnormal, borderline). If abnormal also reason and clinically significance is collected

dECG parameters are assigned to analysis visits and study phases as described in section 3.1.2 and section 3.1.3 respectively. Evaluations with missing or partially missing dates cannot be imputed to any study phase and analysis visit.

dECG last observation on treatment is defined as last available value among those in the on-treatment study phase.

Change from baseline is defined as the post-baseline visit value minus the baseline value.

Additionally, dECG values will be classified as normal (if value is within normal reference range), low (if value is below the normal reference range), and high (if value is above the normal reference range) according to the below normal reference ranges:

Table 14 dECG normal reference ranges

Parameter	Normal Reference Ranges
PR interval	110 – 220 msec
QRS duration	75 – 115 msec
QT interval	320 – 450 msec
Heart rate	50 – 100 beats/min
QTcB interval	320 – 450 msec
QTcF interval	320 – 450 msec

QTcF intervals are classified also as:

- >=450 msec
- >=480 msec
- >=500 msec

QTcF increases respect to baseline are classified as:

- >=30 msec
- >=60 msec
- >=90 msec

3.3.2 Secondary efficacy endpoints

Secondary efficacy endpoints are:

- Hepatic fat fraction (HFF) as assessed by MRI-PDFF
- Other related imaging parameters as assessed by MRI
- Circulating markers of hepatic inflammation
- Immunogenicity
- Weight, BMI and waist and hip circumference

3.3.2.1 Hepatic fat fraction (HFF) as assessed by MRI-PDFF

Hepatic fat fraction (HFF) is assessed by MRI-PDFF in a central external laboratory. HFF is assigned to the analysis visits as described in section 3.1.2. Measurements with missing or partial missing dates are not assigned to any analysis visit. Change from baseline is defined as the post-baseline visit value minus the baseline value; percent change from baseline is calculated as the visit value minus the baseline value dived by the baseline value *100.

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3.3.2.3 Circulating markers of hepatic inflammation

Circulating markers of hepatic inflammation are:

- alanine aminotransferase (ALT)
- aspartate aminotransferase (AST)
- gamma glutamyl transferase (GGT)

These parameters are tested in a central external laboratory. All these parameters are assigned to the analysis visits as described in section 3.1.2. Measurements with missing or partial missing dates are not assigned to any analysis visit.

ALT, AST and GGT below the LLOQ for which the exact value cannot be determined, will be replaced with the LLOQ divided by the squared root of 2.

After the LLOQ replacement, change from baseline is defined as the post-baseline visit value minus the baseline value; percent change from baseline is calculated as the visit value minus the baseline value dived by the baseline value *100.

3.3.2.4 Immunogenicity

Immunogenicity parameters are:

- Anti-drug antibody (ADA)
- Immunogenicity titer
- ADA cross-reactivity to GLP-1
- ADA cross-reactivity to glucagon

These parameters are tested in an external laboratory. 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. All these parameters are assigned to the analysis visits as described in section 3.1.2. Measurements with missing or partial missing dates are not assigned to any analysis visit.

ADA positive sample with titers below the LLOQ (<=15) will be replaced with the LLOQ (15).

3.3.2.5 Weight, BMI and waist and hip circumference

Waist to hip ratio is calculated as waist measurement divided by hip measurement. Measurements should be done the same day. Weight (kg), BMI (kg/m2) , waist and hip circumference (cm) and waist to hip ratio are assigned to analysis visits as described in section 3.1.2. Measurements with missing or partial missing dates are not assigned to any analysis visit. Change from baseline is defined as the post-baseline visit value minus the baseline value; percent change from baseline is calculated as the visit value minus the baseline value dived by the baseline value *100.

3.3.3 Exploratory endpoints

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3.4 Exposure and treatment compliance

As per study protocol, subjects start the subcutaneous (SC) injections of the study IP at day 1. From day 1 to day 7 (included) the injections are performed at site. Starting from day 8, study IP is dispensed to the subject for self-administration at home. Dispensation visits are:

- Day 8
- Day 22
- Day 36
- Day 50
- Day 64
- Day 78
- Day 92
- Day 106
- Day 120

At the dispensation visits the site provide the subject with the number of vials required from the current visit (included) and up to the next visits (excluded) considering that the Subjects should self-inject 1 vial per day. Subjects must return any unused investigational product, and the sharps bin, at their next visit to the clinical site. Number of dispensed vials and number of returned vials are collected in CRF at each dispensation visits.

Except for the first week, for all the other in-site visits the study IP is administered by site personnel taken the kit from the kit stock of vials dispensed.

3.4.1 Exposure

Exposure (days) is calculated only for subjects in the as-treated population as the total number of days on study drug (i.e., gaps in dosing due to study drug interruption will not be taken-out from the calculation). Exposure is calculated as the study drug dose last date minus study drug dose first date plus one. If any of the first or last dates are missing or partially missing, then imputed dates will not be used, and study drug exposure is set to missing.

Actual exposure (days) is calculated as the total number of days of effective study drug intake (i.e., gaps in dosing due to study drug interruption will be taken-out from the calculation). In this way, the subject's dosing can be reduced to a series of unbroken intervals within each, the exposure is calculated as study drug dose stop date minus the study drug dose start date plus one. Actual exposure is then derived as the sum of exposures over all the unbroken intervals.

If any of the start or stop dates are missing or partially missing for an interval, study drug exposure for that interval is set to missing. Actual exposure is the sum over only the intervals where drug exposure was not set to missing.

Cumulative exposure and cumulative actual exposure (day) is also computed based on exposure, using the following duration (days) categories:

- >=8
- >=22
- >=36
- >=50
- >=64
- >=78
- >=92
- >=106
- >=120

3.4.2 Compliance

Overall compliance to the IP is calculated only for subjects in the as-treated population.

The percent compliance is defined as the total number of vials consumed divided by the total number of vials that should have been taken where, total number of vials consumed will be calculated as: Total number of vials dispensed – Total number of vials returned and the total number of vials that should have been taken is the exposure in days.

No replacement of missing data is performed. Therefore, if one of the total number of vials dispensed, total number of vials returned, or duration of exposure is missing the resulting compliance is missing.

Compliance is also categorized as:

- < 80%

- ≥ 80% to < 120%
- ≥ 120%

3.5 Concomitant medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as restricted and prohibited as listed in the study protocol and detailed (coding and indication wherever applicable) in the in the Integrated Data Review Plan (IDRP)

The WHO-DD March 2019 B3 Global or higher is used to classify medications by WHO Anatomical Therapeutic Chemical (ATC) classification of ingredients.

The imputation method described in section 3.1.1.5 is used in case of medication stop date partially missing. Completely missing stop date are not be imputed. Both, completely missing and partially missing concomitant medication start dates are not imputed.

After the end date imputation, the medications will be classified as either prior or concomitant (but not both) according to its stop date. Prior medication is defined as any medication with a stop date prior to the first dose of study drug (exclusive). Concomitant medication is defined as any medication with a stop date on or after the first dose of study drug, or any medication that is ongoing at study end. Medications with completely missing stop date are classified as concomitant.

Prohibited and restricted concomitant medications are confirmed and flagged by the study physician in accordance with the study protocol.

4 ANALYSIS METHODS

4.1 General principles

Data will be summarized using descriptive statistics, by treatment group which consist of MEDI0382 300 μg, MEDI0382 600 μg and placebo, where the placebo group includes the 2 doses of 300 μg and 600 μg of placebo. Data will be summarized at each visit.

For continuous variables, descriptive statistics will include the number of subjects (n), mean, SD, median, minimum and maximum.

For categorical variables and unless otherwise specified, the number and percentages of subjects by categories will be tabulated. Percentages will be calculated based on the number of subjects with no missing data, i.e., will add up to 100%. Categories with count of zero will be not displayed.

All efficacy, exploratory and safety endpoints will be summarized by treatment group and at each visit as appropriate using descriptive statistics as above. Unscheduled visits will be only listed. For continuous variables, descriptive statistics will be summarized for the observed values, the changes from baseline and the percent change from baseline.

Changes from baseline, in certain categorical variables will be summarized using shift tables. The number and percent of subjects within each treatment group will be generated for each category post-baseline by baseline category.

If not otherwise specified, all the analyses will include the post IP-discontinuation data for those subjects who discontinue from study treatments but are still followed up for their scheduled visits.

The following statistical models will be used to compare MEDI0382 300 μg versus placebo and MEDI0382 600 μg versus placebo for some of the study endpoints:

4.1.1 Analysis of covariance (ANCOVA)

The ANCOVA model will be used to fit change and percent change at week 12 and week 19. Data used in the model are data from baseline and the scheduled tested visit. The group of treatment will be considered as a fixed effect of the model while the baseline value as covariate. Comparisons of MEDI0382 300 μg versus placebo and MEDI0382 600 μg versus placebo will be assessed within the same model. The restricted maximum likelihood (REML) approach will be used for the estimation of the variance and covariance parameters of the linear mixed model; two-sided difference test, with alpha level at 5% will be used for the comparisons and for the t-type confidence interval calculation.

Unless otherwise specified, last observation carried forward (LOCF) method will be applied to handle missing data, that is, a missing endpoint will be replaced with the last available post-baseline measurement prior to the missing endpoint.

The residual errors on the model will be evaluated for Normality using residual panel plots in order to validate the model results.

The reportable results from the model will be:

- The least-square means (LSmeans) and their standard errors for each group
- The difference between active groups and placebo (LSmean difference) together with its confidence interval (CI)
- The p-value for the difference between active groups and placebo

For exploratory endpoints, if the parameter results to be normally distributed, the variable fitted in the model will be the change from baseline; the ANCOVA model and the reportable results will be those described above.

On the other hand, if the parameter results to be log-normally distributed, the variable fitted in the model will be the change from baseline in logarithmical scale. Change from baseline in logarithmical scale is defined as the log-transformation of the post-baseline visit value minus the log-transformation of the baseline value.

The ANCOVA model will be as described above but the reportable results from the model will be:

- Back transformed LSmeans for each group, which correspond to the estimated percent change from baseline; back transformed LSmeans is derived as [EXP(LSMean)-1]*100,
- 95%CI of the back transformed LSmeans for each group; 95%CI of the back transformed LSmeans is derived as [EXP(Lower)-1]*100; [EXP(Upper)-1]*100.
- The ratio between active groups and placebo; the ratio is calculated as EXP(LSMean differnce)*100
- The 95%CI of the ratio; the 95%CI of the ratio is calculated as [EXP(Lower)]*100; [EXP(Upper)]*100.
- P-value

To be noted that a ratio lower than 1 means that the active group shows a higher decrease (or a lower increase) compared to the placebo group. On the other hand, a ratio greater than 1 means that the active group shows a lower decrease (or a higher increase) compared to the placebo group.

4.1.2 Sensitivity analysis 1 – the mixed model repeated measures (MMRM)

The sensitivity analysis 1 will be used only at final analysis and will consists on fitting a MMRM to percent change from baseline. Tested visits within the MMRM model are week 12 and week 19. Data used in the model come from all previous available scheduled visits. Fixed factors of the model will be treatment, visit and treatment*visit interaction. The baseline value will be used as covariate. Visit within subject will be considered as repeated measurements. Comparisons of MEDI0382 300 μg versus placebo and MEDI0382 600 μg versus placebo will be assessed within the same model. The restricted maximum likelihood (REML) approach will be used for the estimation of the variance and covariance parameters of the linear mixed model; two-sided difference test, with alpha level at 5% will be used for the comparisons and for the t-type confidence interval calculation.

The model will use the SP (POW) structure for unequally spaced data variance-covariance matrix as default. Visit will be expressed as planned days to accomplish the variance-covariance matrix estimation.

In case the model will not converge for any reasons, the following back-up solutions will be adopted sequentially:

1. The compound symmetry (CS) will be used instead of the SP (POW)
2. The unstructured (UN) will be used instead of the CS

The residual errors on the model will be evaluated for Normality using residual panel plots in order to validate the model results.

The reportable results from the model will be:

- The least-square means (LSmeans) and their standard errors for each group
- The difference between active groups and placebo (LSmean difference) together with its confidence interval (CI)
- The p-value of the difference

4.1.3 Sensitivity analysis 2 - the Wilcoxon Sum Rank test

Th sensitivity analysis 2 will consist on calculating the Wilcoxon Sum Rank test on percent change at week 12 and week 19. Data used in the model are data from baseline and the scheduled tested visit. Comparisons of MEDI0382 300 μg versus placebo and MEDI0382 600 μg versus placebo will be both assessed using this test.

Unless otherwise specified, last observation carried forward (LOCF) method will be applied to handle missing data, that is, a missing endpoint will be replaced with the last available post-baseline measurement prior to the missing endpoint.

The reportable results will be:

- Median, interquartile range, minimum and maximum of the percent change from baseline for each group
- The p-value for the difference between active groups and placebo

4.1.4 Sensitivity analysis 3

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. Sensitivity analysis 3 will be performed at Interim analysis and at final analysis only for HFF and ALT. Data in the on-treatment phase are:

- For HFF all data done before or on the day of last IP + 14 days
- For ALT all data done before or on the day of last IP + 4 days

4.1.5 Sensitivity analysis 4

The sensitivity analysis 4 will consist of repeating the descriptive analysis and the ANCOVA model on the PP population. It will be performed at Interim analysis and at final analysis only for HFF and ALT.

4.1.6 Logistic model

The logistic model will be used to fit proportion of subjects with post-treatment HFF (absolute) < 5% and proportion of subjects with percent decrease from baseline in HFF ≥ 30% at week 12 and at week 19. Data used in the model are data from baseline and the scheduled tested visit. The group of treatment will be considered as a fixed effect of the model while the baseline value as covariate. Comparisons of MEDI0382 300 μg versus placebo and MEDI0382 600 μg versus placebo will be assessed within the same model. Two-sided difference test, with alpha level at 5% will be used for the comparisons and for the Wald confidence interval calculation.

Unless otherwise specified, last observation carried forward (LOCF) method will be applied to handle missing data, that is, a missing endpoint will be replaced with the last available post-baseline measurement prior to the missing endpoint.

The reportable results from the model will be:

- The odds ratio between active groups and placebo together with its confidence interval (CI) by the exact method
- The p-value for the odds ratio between active groups and placebo

4.2 Analysis of variables

4.2.1 Disposition of subjects

Subject dispositions (number and percentage of subjects enrolled, subjects randomized, subjects who received at least one dose of study IP, subjects who completed the treatment and subjects who completed the study) will be presented in a summary table for each treatment group and overall. A listing including all standardized disposition terms will be also provided for all discontinued subjects. Both, the table and the listing will be based on all enrolled subjects population.

A Summary of COVID-19 study disruptions will be also presented. Listings of subjects affected by pandemic situation and the CTMS issues due to pandemic are also included.

The number of subjects belonging to each analysis population will be presented in a separate summary table for each treatment group. The table will be based on all enrolled subjects population. Listings of all subjects excluded from the ITT population and from the as-treated population will be also provided. The listings will include reason for exclusion from respective population and will be based on all enrolled subjects population.

Randomization code and actual kit are also listed.

4.2.2 Important protocol deviations

The number and percentage of subjects with at least one IPD will be summarized following the NHP categories, for each treatment group and overall.

All IPD will be also listed for all subjects included in the ITT population.

4.2.3 Baseline assessment and other subject-specific characteristics

4.2.3.1 Demographic and subject-specific characteristics

All demographic and subject-specific characteristics reported in section 3.2.1 will be presented in summary tables for each treatment group and overall; Age, height, weight and BMI will be summarized descriptively as continuous variable with n, mean, median, SD, minimum, and maximum; all the other demographic and subject-specific characteristics will be summarized as categorical variables with the number and percentages of subjects by categories. Only the baseline measurement for height, weight and BMI will be considered.

All demographic and subject-specific characteristics will be also provided in listings.

The tables and the listings will be based on the ITT population. Baseline and post-baseline definitions are detailed in section 3.1.2.

4.2.3.2 Medical history

Relevant medical history as described in section 3.2.2 will be presented in summary tables as number and percentages of subjects by System Organ Class (SOC) and Preferred Term (PT) for each treatment group and overall. Subjects with multiple events in the same SOC/PT will be counted only once in that SOC/PT. Subjects with events in more than one SOC/PT will be counted once in each of those SOC/PT. The table will be sorted alphabetically by SOC and PT and will be based on the ITT population.

Diet and exercise history will be presented in summary table for each treatment group and overall. The table will be based on the ITT population.

4.2.3.3 Alcohol use

Alcohol use as described in section 3.2.3 will be presented in summary table as number and percentages of subjects for each treatment group and overall. AUDIT questionnaire as described in section 3.2.3 will be also summarized together with alcohol use, as number and percentages of subjects for each question in the questionnaire. The table will be based on the ITT population.

4.2.4 Primary safety endpoints

4.2.4.1 Adverse events

After having assigned the AEs to the corresponding study phase as described in section 3.3.1.1, the AEs will be summarized for each treatment group. The AEs tables will be based on the as-treated population. Summary tables will include AEs in the on-treatment phase and AEs in the follow-up phase.

Summary tables are listed below.

An overview table containing:

- Number and percentage of subjects with any AEs
- Number and percentage of subjects with any AEs leading to death
- Number and percentage of subjects with any SAEs
- Number and percentage of subjects with any AEs leading to discontinuation of IP
- Number and percentage of subjects with any AEs leading to withdrawal from study

The following summary tables will be presented by SOC and PT:

- The number and percentage of subjects with any AEs
- The number of AEs
- The number and percentage of subjects with AEs with outcome of death,
- The number and percentage of subjects with SAEs
- The number of SAEs

- The number and percentage of subjects with AEs leading to discontinuation.

- The number and percentage of subjects with any AEs by maximum reported intensity.
- The number and percentage of subjects with any AEs and investigator's causality assessment. If a subject has multiple events in the same PT, the event with the strongest relationship will be counted.

The number and percentage of subjects with most common AEs (frequency of >5%) will be presented by PT.

Where number of subjects with AEs are summarized by system organ class (SOC) and/or preferred term (PT) , subjects with multiple events in the same SOC/PT are counted only once in that SOC/PT. Subjects with events in more than 1 SOC/PT are counted once in each of those SOCs/PTs.

Additionally, the following tables will be presented:

- the number of subjects with serious adverse events, by seriousness criteria.
- the number and percentage of subjects with non-serious AEs occurring with a frequency > 5.0% in any treatment group for each SOC and PT. This table will be produced as a separate pdf output to meet clinical trial transparency requirements and not for inclusion in the clinical study report (CSR). It will be delivered at the same time as the CSR outputs.
- the number of subjects with injection site reactions by high level term (HLT) and PT.

A list of key subject information for subjects with AEs with outcome of death, subjects with SAEs, and subjects with AEs leading to discontinuation of IP will be provided. The durations reported in these tables, will be derived only for fully completed dates as below:

- Time from first dose of IP to AE (in days) will be calculated as the AE start date minus date of dose +1.
- Time from first dose to death (in days) will be calculated as the date of death minus date of dose +1.
- The same approach will be used for deriving time from start of treatment to AE becoming serious or discontinuation.
- Time from last dose prior to AE start and last dose prior to death will be calculates as the date of death minus the date of last dose prior to AE/death +1.

Lastly, a specific table presenting the event rate by period for nausea and vomiting and the corresponding bar-charts and line plots will be also provided. The event rate is calculated as:

Total number of events when subjects are on study IP in the selected period divided by the total person-days of exposure to study IP for the whole relevant arm in the selected period. The total person-days of exposure is the sum of all the exposures, in days, of all the subjects who are ever exposed to study IP within the specific period, in the relevant arm, for the selected period.

For numerator calculation during a period (e.g. the first 1-week analysis), if an event is onset at day 1 and ends at day 3, then it will be counted as one event for this period. For numerator

calculation, if an event is onset at day 1 and ends at day 9, then this event will be counted as an event for both week 1 analysis and week 2 analysis. Only on-treatment days (from first dose to last dose of IP) will be included in the denominator calculation of exposure (person-days); consequently, only events on those on-treatment days will be included in the numerator calculation. In the rare case in which there is a gap in dosing of more than 7 days, the inclusion of the AE which started during the gap period and the exposure days calculation should be evaluated case by case.

All the AEs regardless of the study phases will be also listed for all subjects included in the as-treated population.

4.2.4.2 Laboratory evaluation

Laboratory evaluation are described in section 3.3.1.2. Baseline and post-baseline definitions are detailed in section 3.1.2. All tables and listings for laboratory data will be based on the as-treated population and presented for each treatment group.

Laboratory test results for haematology, coagulation, clinical chemistry and urinalysis quantitative parameters will be summarized in SI units with n, mean, SD, median, minimum, and maximum at each visit and for change from baseline. Shifts from baseline to maximum and minimum value during the on-treatment phase will be also presented.

Shifts from baseline to maximum value during the on-treatment phase will be presented for urinalysis qualitative parameters and AST, ALT and total bilirubin in class.

All laboratory data for haematology, coagulation, clinical chemistry and urinalysis will be also presented in listings.

In addition to the tables above also the maximum on-treatment ALT and AST by maximum total bilirubin for assessing Hy's law criteria, the eDISh plot for ALT and total bilirubin, a list of key subject information for subjects with potential Hy's law as described in the study protocol and a list of key subject information for subjects with ALT or AST≥8xULN or total bilirubin ≥2xULN during the on-treatment phase will be presented.

4.2.4.3 Vital signs

Vital signs and ABPM parameters are described in section 3.3.1.3. Baseline and post-baseline definitions are detailed in section 3.1.2. Vital signs tables and listings will be based on the as-treated population and presented for each treatment group.

Vital signs will be summarized descriptively as continuous variables with n, mean, median, SD, minimum, and maximum, at each visit and timepoint within visit and for change from baseline. Orthostatic measures supine are included in this summary table.

Observed values and change from baseline in systolic blood pressure, diastolic blood pressure, heart rate and rate pressure product (RPP) measurements will be also presented in figures with

mean and standard error of the mean (SE). Only measurements done pre-dose will be plotted; orthostatic measures at day 51, 52, 65, 66, 79 and 80 will be not included.

The number of subjects in SBP change categories with maximum heart rate change from baseline > 20 bpm at concurrent visit will be also summarized. Only measurements done pre-dose will be considered; measures at day 51, 52, 65, 66, 79 and 80 will be not included.

All vital signs data, including orthostatic measures at day 51, 52, 65, 66, 79 and 80 will be listed. The listing will include reference ranges and classification of vital signs as normal, low and high.

For systolic blood pressure, diastolic blood pressure, heart rate and rate pressure product an ANCOVA model as described in section 4.1 for change at week 12 and at week 19 will be also presented. Tested visits are the pre-dose measurements at week 12 and at week 19.

ABPM parameters (complete ABPM SBP, complete ABPM DBP, complete ABPM heart rate, complete ABPM RPP, day ABPM SBP, day ABPM DBP, day ABPM heart rate, day ABPM RPP, night ABPM SBP and night ABPM DBP, night ABPM heart rate, night ABPMRPP) will be summarized descriptively as continuous variables with n, mean, median, SD, minimum, and maximum, at each visit and for change from baseline. Summary statistics are calculated excluding values = 0 for heart rate, systolic blood pressure and diastolic blood pressure, values < 80 mmHg for systolic blood pressure and values < 50 or > 120 mmHg for diastolic blood pressure.

Observed values in complete ABPM systolic blood pressure, diastolic blood pressure, heart rate and rate pressure product (RPP) measurements will be also presented in figures with mean and standard error of the mean (SE).

4.2.4.4 dECG

dECG parameters are described in section 3.3.1.4. Baseline and post-baseline definitions are detailed in section 3.1.2. dECG tables and listings will be based on the as-treated population and presented for each treatment group.

dECG parameters (except for the overall evaluation) will be summarized in SI units with n, mean, median, SD, minimum, and maximum, at each visit and for change from baseline.

Number and percentage of subjects within each QTcF intervals classes at any time during the on-treatment phase will be also reported together with number and percentage of subjects within QTcF increase classes at any time during the on-treatment phase.

Overall evaluation will be analysed as shift from baseline to last value in the on-treatment phase.

dECG parameters will be also listed for all subjects. Overall evaluation will be listed for subjects with clinically significant abnormalities.

4.2.5 Secondary efficacy endpoints

4.2.5.1 Hepatic fat fraction (HFF) as assessed by MRI-PDFF

HFF is described in section 3.3.2.1. Baseline and post-baseline definitions are detailed in section 3.1.2. Tables and listings will be based on the ITT population and presented for each treatment group.

HFF will be summarized descriptively as continuous variable with n, mean, median, SD, minimum, and maximum, at each analysis visit and for change and percent change from baseline and separately for subjects who have and don't have type 2 diabetes mellitus. Observed value, change and percent change of HFF will be also presented in figure with mean and standard error of the mean (SE) by visit.

An ANCOVA model as described in section 4.1 for change and percent change of HFF, at week 12 and at week 19 will be also presented. In addition of what reported in section 4.1, also the p-value of the LSmeans is reported for each group.

An ANCOVA model as described above for change and percent change of HFF, at week 12 and at week 19 will be also presented for subjects in active treatment (MEDI0382 300 µg or MEDI0382 600 µg) versus placebo.

Sensitivity analyses 1, 2, 3 and 4 as described in section 4.1 will be also performed with the aim to consolidate the results obtained with the previous ANCOVA model.

HFF will be also reported in listing.

4.2.5.2 Other related imaging parameters as assessed by MRI

All the other related imaging parameters are described in section 3.3.2.2. Baseline and post-baseline definitions are detailed in section 3.1.2. Tables and listings will be based on the ITT population and presented for each treatment group.

All parameters will be summarized descriptively as continuous variable with n, mean, median, SD, minimum, and maximum, at each analysis visit and for change and percent change from baseline.

An ANCOVA model as described in section 4.1 for change and percent change for each parameter, at week 12 and at week 19 will be also presented.

All parameters will be also reported in listing.

4.2.5.3 Circulating markers of hepatic inflammation

ALT, AST and GGT are described in section 3.3.2.3. Baseline and post-baseline definitions are detailed in section 3.1.2. Tables and listings will be based on the ITT population and presented for each treatment group.

ALT, AST and GGT will be summarized descriptively as continuous variable with n, mean, median, SD, minimum, and maximum, at each analysis visit and for change and percent change from baseline. Observed value, change and percent change of ALT will be also presented in figure with mean and standard error of the mean (SE) by visit.

An ANCOVA model as described in section 4.1 for change and percent change, at week 12 and at week 19 will be also presented.

All circulating markers will be also reported in listing.

For the alanine aminotransferase (ALT) the sensitivity analyses 1, 2, 3 and 4 as described in section 4.1 will be also performed with the aim to consolidate the results obtained with the above ANCOVA model.

4.2.5.4 Immunogenicity

Immunogenicity parameters are described in section 3.3.2.4. Baseline and post-baseline definitions are detailed in section 3.1.2. Immunogenicity parameters tables and listings will be based on the as-treated population and presented for each treatment group.

ADA, ADA cross-reactivity to GLP-1 and ADA cross-reactivity to glucagon will be summarized as categorical variables with the number and percentages with a positive result at the specific visit. ADA titers will be summarized descriptively as continuous variable, only for ADA positive tests, with median, interquartile range, minimum, and maximum, at each analysis visit.

ADA, ADA cross-reactivity to GLP-1 and ADA cross-reactivity to glucagon will be also summarized including the following:

- ADA prevalence: subjects who are ADA positive at any visit (including baseline)
- Subjects who are ADA positive at baseline only
- Subjects who are ADA positive at baseline and have at least one positive value post baseline
- Subjects who are not ADA positive at baseline and have at least one positive value post-baseline only (treatment-induced ADA)
- Subjects who are persistently positive; persistently positive is defined as at least 2 post-baseline ADA positive measurements (with >=16 weeks apart) or an ADA positive result at the last available assessment
- Proportion of subjects who are transiently positive; transiently positive is defined as at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive
- Proportion of subjects who are treatment-boosted ADA; treatment-boosted ADA is defined as baseline ADA titer that was boosted to a 4-fold or higher level following drug administration
- ADA incidence (treatment-emergent ADA), defined as the sum of treatment-induced ADA (post-baseline positive only) and treatment-boosted ADA

Post baseline includes on-treatment and follow-up phases.

All immunogenicity parameters will be also reported in listing.

4.2.5.5 Weight, BMI and waist and hip circumference

Weight, BMI, waist circumference and waist to hip ratio are described in section 3.3.2.5. Baseline and post-baseline definitions are detailed in section 3.1.2. Tables and listings will be based on the ITT population and presented for each treatment group.

Weight, BMI, waist circumference and waist to hip ratio will be summarized descriptively as continuous variables with n, mean, median, SD, minimum, and maximum, at each analysis visit and for change and percent change from baseline.

Observed value, change and percent change of weight will be also presented in figure with Mean and standard error of the mean (SE) by visit.

An ANCOVA model as described in section 4.1 for change and percent change of weight and for change in BMI will be also presented.

Weight, BMI, waist circumference and waist to hip ratio will be also reported in listing at each visit and for change from baseline.

4.2.6 Exploratory endpoints

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

5 INTERIM ANALYSES

An unblinded interim analysis (IA) 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. These analyses will not have any impact on the overall type-1 error because no changes will be made to the trial based on the outcome of the analyses. The purpose with the interim analyses is to trigger external activities not connected to the trial. Additional details on the interim analysis procedures (i.e. data cut-off rules, data cleaning, nomination of the unblinded biometric team and the unblinding review committee team (URC) and the operational procedures used to protect the blinding) are given in the interim analysis charter.

The interim analysis is focused on:

- Description of the population
- Overview of the safety variables
- Overview of efficacy parameters

5.1 Description of the population

Subject dispositions and demographic and subject-specific characteristics will be presented in summary tables as reported in section 4.2.1 and 4.2.3.1 respectively. Overall compliance and compliance categories will be presented in a summary table as reported in section 4.2.7.2.

5.2 Overview of the safety variables

5.2.1 Adverse events

An overview table will be presented as reported in section 4.2.4.1.

The following summary tables will be presented by SOC and PT:

- The number and percentage of subjects with any AEs
- The number and percentage of subjects with AEs with outcome of death,
- The number and percentage of subjects with SAEs
- The number and percentage of subjects with AEs leading to discontinuation.

The following summary tables will be presented by PT:

- The number and percentage of subjects with most common AEs.
- The number and percentage of subjects with any AEs by maximum reported intensity
- Number of subjects with adverse events, by preferred term and relationship as assessed by investigator.

Additionally, the following tables will be presented:

- the number of subjects with serious adverse events, by seriousness criteria.
- the number and percentage of subjects with non-serious AEs occurring with a frequency > 5.0%
- the number of subjects with injection site reactions by high level term (HLT) and PT.

Lastly, a specific table presenting the event rate by period for nausea and vomiting and the corresponding bar-charts will be also provided.

All these tables are described in section 4.2.4.1.

5.2.2 Laboratory evaluation

Laboratory test results for haematology, coagulation, clinical chemistry and urinalysis quantitative parameters will be summarized descriptively.

Shifts from baseline to maximum and minimum value during the on-treatment phase will be also presented.

Shifts from baseline to maximum value during the on-treatment phase will be presented for urinalysis qualitative parameters, AST and ALT and total bilirubin in class.

In addition to the tables above also the maximum on-treatment ALT and AST by maximum total bilirubin for assessing Hy's law criteria, the eDISh plot for ALT and total bilirubin , a list of key subject information for subjects with potential Hy's law as described in the study protocol and a list of key subject information for subjects with ALT or AST≥8xULN or total bilirubin ≥2xULN during the on-treatment phase will be presented.

All these tables are described in section 4.2.4.2.

5.2.3 Vital signs

Vital signs will be summarized descriptively.

Observed values and change from baseline in systolic blood pressure, diastolic blood pressure, heart rate and rate pressure product (RPP) measurements will be also presented in figures.

The number of subjects in SBP change categories with maximum heart rate change from baseline > 20 bpm at concurrent visit will be also summarized.

For systolic blood pressure, diastolic blood pressure, heart rate and rate pressure product the ANCOVA model for change will be also presented.

ABPM parameters will be summarized descriptively. Observed values in complete ABPM systolic blood pressure, diastolic blood pressure, heart rate and rate pressure product (RPP) measurements will be also presented in figures.

All these tables are described in section 4.2.4.3.

5.2.4 dECG

dECG parameters (except for the overall evaluation) will be summarized descriptively as reported in section 4.2.4.4.

5.3 Overview of efficacy parameters

5.3.1 Hepatic fat fraction (HFF) as assessed by MRI-PDFF

HFF will be summarized descriptively. Observed value, change and percent change of HFF will be also presented in figures.

The ANCOVA model for change and percent change of HFF will be also presented.

Sensitivity analyses 1, 2, 3 and 4 will be also performed.

All these tables are described in section 4.2.5.1.

5.3.2 Circulating markers of hepatic inflammation

ALT, AST and GGT will be summarized descriptively. Observed value, change and percent change of ALT will be also presented in figures.

The ANCOVA model for change and percent change will be presented for ALT. The ANCOVA model for percent change will be also presented for AST and GGT.

Sensitivity analyses 1, 2, 3 and 4 will be performed for ALT.

All these tables are described in section 4.2.5.3.

5.3.3 Immunogenicity

ADA will be summarized as categorical variables. ADA titer will be summarized descriptively. ADA, will be also summarized in an ad-hoc table. All these tables are described in section 4.2.5.4.

5.3.4 Weight

Weight will be summarized descriptively as continuous variable. Observed value and percent change of weight will be also presented in figures. The ANCOVA model for percent change from baseline will be also presented.

All these tables are described in section 4.2.5.5.

5.3.5 Biomarkers

CK18, ELF, Insulin, Plasma glucose, HbA1c, C-peptide, FIB-4, APRI and NFS will be summarized descriptively as continuous variable. The ANCOVA model for change from baseline will be also presented.

All these tables are described in section 4.2.6.1.

5.3.6 Lipid parameters

All parameters except Lipidomics - NAFLD will be summarized descriptively as continuous variable. The ANCOVA model for change from baseline will be also presented.

All these tables are described in section 4.2.6.2.

5.3.7 Hepatic fat fraction (HFF) as assessed by MRI-PDFF

Proportion of subjects with post-treatment HFF (absolute) < 5% and proportion of subjects with percent decrease from baseline in HFF ≥ 30% will be summarized descriptively as categorical variables as described in section 4.2.6.6.

6 AD-HOC SAFETY REVIEW

Upon request from the Sponsor, an unblinded ad-hoc safety review can be performed at any time during the study. Aim of this review will be to evaluate product safety only. No changes will be made to this study unless a safety signal is observed. The analysis will be carried on using the data available at the date of request. No additional external data transfer are planned for this analysis.

Additional details on the Ad-hoc safety procedures (i.e. data cut-off rules, data cleaning, nomination of the unblinded biometric team and of the independent monitoring committee

team and the operational procedures used to protect the blinding) are given in the interim analysis charter.

Reporting of the results will depend on the scope of the ad-hoc safety review. Pre-specified options for the scope (minimum, medium or maximum) are described below.

6.1 Minimum scope

In the minimum scope the following summary tables will be presented.

6.1.1 Description of the population

Subject dispositions and demographic characteristics except height weight, BMI and type 2 diabetes mellitus will be presented in summary tables as reported in section 4.2.1 and 4.2.3.1 respectively.

6.1.2 Adverse events

An overview table will be presented as reported in section 4.2.4.1.

The following summary tables will be presented by SOC and PT:

- The number and percentage of subjects with AEs with outcome of death,
- The number and percentage of subjects with SAEs The number and percentage of subjects with AEs leading to discontinuation.

The following summary tables will be presented by PT:

- The number and percentage of subjects with most common AEs.
- The number and percentage of subjects with any AEs by maximum reported intensity.
- The number and percentage of subjects with any AEs and investigator's causality assessment.

All these tables are described in section 4.2.4.1.

6.2 Medium scope

In the medium scope, in addition to the summary tables presented for the minimum scope above, also the following tables will be presented:

6.2.1 Adverse events

The number of subjects with injection site reactions by high level term (HLT) and PT.

A specific table presenting the event rate by period for nausea and vomiting and the corresponding bar-charts will be also provided.

All these tables are described in section 4.2.4.1.

6.2.2 Vital signs

Vital signs will be summarized descriptively as described in section 4.2.4.3.

6.3 Maximum scope

In the maximum scope, in addition to the summary tables presented for the medium scope above, also the following tables will be presented:

6.3.1 Laboratory evaluation

Laboratory test results for haematology, coagulation, clinical chemistry and urinalysis quantitative parameters will be summarized descriptively.

Shifts from baseline to maximum and minimum value during the on-treatment phase will be also presented.

Shifts from baseline to maximum value during the on-treatment phase will be presented for urinalysis qualitative parameters, AST and ALT and total bilirubin in class.

In addition to the tables above also the maximum on-treatment ALT and AST by maximum total bilirubin for assessing Hy's law criteria, the eDISh plot for ALT and total bilirubin , a list of key subject information for subjects with potential Hy's law as described in the study protocol and a list of key subject information for subjects with ALT or AST≥8xULN or total bilirubin ≥2xULN during the on-treatment phase will be presented.

All these tables are described in section 4.2.4.2.

6.3.2 Vital signs

Observed values and change from baseline in systolic blood pressure, diastolic blood pressure, heart rate and rate pressure product (RPP) measurements will be also presented in figures.

The number of subjects in SBP change categories with maximum heart rate change from baseline > 20 bpm at concurrent visit will be also summarized.

For systolic blood pressure, diastolic blood pressure, heart rate and rate pressure product the ANCOVA model for change at week 12 and week 19 will be also presented.

ABPM parameters will be summarized descriptively. Observed values in complete ABPM systolic blood pressure, diastolic blood pressure, heart rate and rate pressure product (RPP) measurements will be also presented in figures.

All these tables are described in section 4.2.4.3.

6.3.3 dECG

dECG parameters (except for the overall evaluation) will be summarized descriptively as reported in section 4.2.4.4.

7 CHANGES OF ANALYSIS FROM PROTOCOL

This SAP is based on study protocol D5671C00002 Amendment 5 dated 21/04/2020. Any further amendment of the study protocol which can have an impact on the SAP will lead to an amendment of this document. Changes of analysis from D5671C00002 Amendment 5 dated 21/04/20120 are listed here below:

Section 2 – Objectives and endpoints

- In this section is stated that all the endpoints are analyses at week 19. Analyses at week 12 are also reported.

Section 2.1 - Primary Objective and Associated Endpoint

- In this section is stated that the primary safety endpoints are the incidences of treatment emergent adverse events and serious adverse events. In this SAP it is specified that also laboratory data, vital signs and dECG are included in the safety analysis and therefore are considered as primary safety endpoints.

Section 2.2 - Secondary Objectives and Associated Endpoints

- In this section it is stated that one of the objectives is to assess the dose response of MEDI0382 on pharmacodynamic parameters. However, pharmacodynamic parameters dose-response is already evaluated through the other primary and secondary analyses which are performed by treatment group. No additional analyses are included in this report about this objective.
- Circumference is considered secondary objectives in this SAP together with body weight and BMI while the study protocol mentions only body weight and BMI.

CCI

Section 4.3.6 Clinical Laboratory Tests

- Calcitonin, TSH, amylase and lipase are added in the serum chemistry list of parameters.

Tables 5, 6, 7 and 8 Vital signs

- Rate pressure product (RPP) was not mentioned, however, it is added in the list of vital signs parameters and in the statistical analysis.

4.8.3.1 Efficacy Analysis

- In this section is stated that percent change from baseline to Week 19 will be analysed using analysis of covariance (ANCOVA). However, for all the secondary efficacy parameter for which the ANCOVA model is used, both change and percent change are tested and also the ANCOVA test at Week 12 is performed.

- Added normality test for all exploratory parameters before to use the ANCOVA model. Moreover, for lognormal parameters added that the ANCOVA model is fitted on log-transformed variable and then the results are transformed back for reportable purpose.

- In this section is stated that the mixed model for repeated measures (MMRM) approach should use the unstructured covariance. However, because the visits are not equally spaced, the SP (POW) structure is used. In case the model will not converge for any reasons, the following back-up solutions will be adopted sequentially: 1 - The compound symmetry (CS) will be used instead of the SP (POW); 2 - The unstructured (UN) will be used instead of the CS

4.8.3.2 Additional Analyses of the Efficacy Endpoint

- In this section is stated that additional MMRM analysis is performed only on percent change from baseline to Week 19. However, it is performed also on percent change from baseline to Week 12. Moreover, the same additional analysis is performed on ALT.

Section 4.8.4.2 Analysis of Clinical Laboratory Parameters

- This section stated to analyse the Hepatic safety analyses with Mean changes from baseline to end of treatment in ALT and AST levels. However, the mean change is reported at al visits and not at end of treatment.

8 REFERENCES

N.A.

9 APPENDIX

9.1 Appendix 1 Changes made to the SAP after initial sign-off

9.1.1 Version 1.0

NA

9.1.2 Version 2.0

Section 2.1

Specified how to derive actual treatment.

Section 2.2

Added the list of relevant IPD to be used for the derivation of the PP population.

Section 3.1.2

Added that lipidomic measurements collected on day 1 are always considered collected before the first dose of IP because the time of collection is not reported in CRF but they should always be collected pre-dose as per protocol.

Section 3.3.1.1 Adverse event

For the sake of clarity, the AEs allocation to the study phases was rephrased. No change in the content of the algorithm.

Section 3.3.1.2 Laboratory evaluation

Added the complete list of parameters to be included in the white blood cell count with percent differential.

Section 3.3.1.3 Vital signs

Adjusted normal values for SBP and DSP to reflect common definitions.

Added the acceptance criteria for ABPM records.

Added RPP calculation also for ABPM.

Section 3.3.2.4 Immunogenicity

Delete description of change and percent change since not used for ADA data

CCI [redacted]

[redacted]

Section 4.1 General principles and section 4.2.5

Added the reportable results in case of log-Normal distributed variables.

Section 4.1.3 Sensitivity analysis 2 - the Wilcoxon Sum Rank test

Added IQR to the reportable results

Section 4.2 Analysis of variables

Values below the LLOQ will be replaced with LLOQ/squared root (2).

Section 4.2.4.1 Adverse event

Added a table to summarize the number of subjects with injection site reactions.

Defined most common AE as grater than 5%

Section 4.2.4.2 Laboratory evaluation

Added a shift table from baseline for bilirubin, the eDISh plot with ALT vs total bilirubin and a list of key subject information for subjects with potential ALT or AST≥8xULN or total bilirubin ≥2xULN during the on-treatment phase.

Section 4.2.4.3 Vital signs

Added figure on observed values and change from baseline for systolic blood pressure and diastolic blood pressure.

Added a table which summarize the number of subjects in SBP change categories and with maximum pulse change from baseline >= 20 bpm.

For the sake of clarity, the ABPM Summary statistics calculation text was rephrased.

Added RPP ABPM analysis (descriptive statistics and figures)

Section 4.2.5.4 Immunogenicity

Adjusted on ADA AZ standards tables.

Section 4.2.6 Exploratory endpoints

CCI [redacted]

Section 5 Interim analysis

Modified as per final analysis – section 4 - for the concerning tables. Added tables on number and percentage of subjects with any AEs by maximum reported intensity and ABPM variables, over time.

Referenced all repeated details to previous sections.

Added tables for biomarkers and lipid parameters, sections 5.3.5 and 5.3.6.

Section 6 Ad-hoc safety review

Added the entire section.

Changes due to protocol amendment 4:

Added FIB-4, APRI, BARD score, NFS, and FLI in biomarkers exploratory endpoints.

Deleted adiponectin high in lipid parameters

Added a sensitivity analysis for HFF and ALT based on the Wilcoxon Sum Rank test.

Weight and BMI promoted to secondary objectives

Added proportions related to HFF as exploratory objective (logistic model)

Changes due to protocol amendment 5:

Visit windows for MRI at day 78 and at day 133 enlarged

Interim analysis when approximately 39 subjects will be completed approximately 19 week of treatment.

MRI at screening can be repeated if the first measurements is not adequate.

9.1.3 Version 3.0

Section 3.1.2 Analysis visit windows – table 9:

AVISIT derivation: added range for AVISIT derived from CRF visits

9.1.4 Version 4.0

Section 4.2.5.1 Hepatic fat fraction (HFF) as assessed by MRI-PDFF:

Added for HFF only: descriptive statistics by T2DM, p-values for change from baseline within each group and comparison between all active patients versus placebo

9.1.5 Version 5.0

Section 3.3.2.4 Immunogenicity

Specified that also for borderline positive ADA titer values are replaced.

Sections 3.2.2 and 4.2.3.2 Medical history

Deleted the Disease related medical history page because not recorded correctly in the CRF.

Section 3.3.3.1 Biomarkers

CCI [redacted]

CCI [redacted]

CCI [redacted]

Section 4.2.1 Disposition of subjects

Added COVID tables

Section 4.2.4.1 Adverse events

Added SOC in table S10 and S11.

Added line plots for nausea and vomiting.

Section 4.2.5.4 Immunogenicity

ADA tables and listing changed the referring population, as-treated population used instead of ITT.

SIGNATURE PAGE

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