Statistical Analysis Plan

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I confirm that I have reviewed this document and agree with the content.

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
ALT	Alanine aminotransferase
ApoA1	Apolipoprotein A-1
ApoB	Apolipoprotein B
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BBR	Berberine
bid or b.i.d	Twice per day
BMI	Body Mass index
CI	Confidence Interval
C_{max}	Maximum concentration
CRF	Case Report Form
CRP	C-Reactive Protein
ECG	Electrocardiogram
FPG	Fasting plasma glucose
G6PD	Glucose-6-Phosphate Dehydrogenase
HbA1c	Glycosylated hemoglobin
HDL-C	High Density Lipoprotein Cholesterol
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
LDL-C	Low Density Lipoprotein Cholesterol
LLN	Lower Limit of Normal
Lp(a)	Lipoprotein(a)
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N/A	Not Applicable
NEFA	Non-Esterified Fatty Acid (synonymous with FFA)

Abbreviation	Description
NYHA	New York Heart Association
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred Term
QTc	Corrected QT Interval
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
$t_{1/2}$	half-life
TEAE	Treatment Emergent Adverse Event
TLF	Table, Listing and Figure
T_{max}	Time to maximum serum concentration
T_{min}	Time to minimum serum concentration
TSH	Thyroid-stimulating hormone
UDCA	Ursodeoxycholic acid
ULN	Upper limit of normal
WHODrug	World Health Organization Drug Dictionary
WNL	Within Normal Limits

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. RESPONSIBILITIES

Syneos Health will perform statistical analyses and are responsible for the production and quality control of all tables, figures and listings pre-defined in SAP Version 1.0. Boston Biostatistics Research Foundation will perform statistical analyses and are responsible for the production and quality control of additional post-hoc tables, figures and listings defined in SAP Version 2.0.

Pharmacokinetic (PK) analysis will be carried out by HighTide Biopharma Pty Ltd and will be documented in a separate file. External vendor (TetraQ) will conduct the PK analysis using the concentration data on behalf of the Sponsor. The vendor will prepare a separate SAP for that purpose.

2.2. TIMINGS OF ANALYSES

The primary analysis of safety and tolerability and pharmacodynamics is planned after all subjects complete the final study visit or terminate early from the study.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

The primary objective for this study is to assess the safety and tolerability of multiple ascending dose levels of HTD1801 in participants with hypercholesterolemia.

3.2. SECONDARY OBJECTIVES

There are four secondary pharmacokinetic (PK)/pharmacodynamic (PD) objectives for this trial.

1) To assess the PK profile of HTD1801 after repeat doses as assessed by derived PK parameters including but not limited to:

   - Plasma half-life of HTD1801 components ($t_{1/2}$)
   - Maximum plasma concentration of HTD1801 components (C_{max})
   - Minimum plasma concentration of HTD1801 components (C_{min})
   - Time to C_{max} (T_{max})
   - Time to C_{min} (T_{min})

2) To determine the effects of HTD1801 on lipid metabolism:

   - Fasting lipid metabolism and atherogenic biomarkers as assessed by actual values and change from baseline of:
     - Low-density lipoprotein-C (LDL-C)
     - Non-high-density lipoprotein-C (non-HDL-C)
     - Total cholesterol (TC), HDL-C, and TC/HDL-C ratio
     - Apolipoprotein B (ApoB) and A-1 (ApoA1)
     - Triglycerides and non-esterified fatty acid (NEFA)
     - Serum proprotein convertase subtilisin/kexin type 9 (PCSK9)
     - C- reactive protein (CRP) measured using a high-sensitivity assay
     - Lipoprotein(a) [Lp(a)]

3) To determine the effects of HTD1801 glucose metabolism:

- Glycosylated hemoglobin (HbA1c) levels
- Markers of fasting glucose metabolism as assessed by actual values and change from baseline of:
  - Fasting plasma glucose (FPG)
  - Fasting serum insulin
  - C-peptide

4) To determine the effects of HTD1801 on markers of liver function

- Actual values and change from baseline in Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST)

3.3. BRIEF DESCRIPTION

This is a randomized, double-blind, placebo controlled, multicenter, multiple ascending dose (MAD) study with the primary objective of evaluating the safety and tolerability of HTD1801 in overweight to obese participants with hypercholesterolemia.

There are three planned dose escalation cohorts. Each cohort will consist of 16 participants, randomized 3:1 to receive either HTD1801 or placebo. The three planned cohorts may enroll up to 48 participants. Participants who withdraw from the trial may be replaced following consultation with the Sponsor. The cohorts will be enrolled sequentially. The ascending dose cohort may be initiated once it has been established that HTD1801 is well-tolerated at the previous dose, independent of preliminary efficacy findings.

Participants in each cohort will participate in a Screening Visit, two 2-day in-house visits separated by a 4-week Outpatient Period (includes one Out-Patient Visit), and one Follow-up telephone contact. Eligible participants who are currently taking anti-dyslipidemia medications must consent, with approval of their physician, to discontinue these medications and undergo a Washout Period, prior to completion of screening and participating in the trial.

The washout period is at least 4 weeks prior to dosing.

During the first in-house Visit 1, participants will undergo baseline glucose and lipid metabolic assessments on the day prior to dosing, receive their first dose of study drug on Day 1, and undergo post-dosing safety monitoring. On Day 2 the participants will receive their second dose of study medication in the morning, and receive dietary counseling and instruction for taking study drug during the Outpatient Period.

The Outpatient Period will last for approximately 3 weeks. There will be one outpatient visit during this period, on Day 14 (±3 days), to obtain samples for PK, glucose and lipid metabolism biomarkers, liver function biomarkers, vital signs, safety evaluations and to review treatment compliance.

The second in-house Visit 2 will begin on Day 27 (±3 days), followed by discharge on the morning of Day 29 (±3 days). During this period participants will undergo evaluations for PK, glucose and lipid metabolism biomarkers, liver function biomarkers, vital signs, safety evaluations and to review treatment compliance, post-dosing metabolic assessments. A safety Follow-up phone call will occur on Day 42±3. The trial is expected to take approximately ten weeks for each participant from Screening through Follow-up.

Each in-house visit is expected to last approximately 2 days.

3.4. SUBJECT SELECTION

This trial will be performed in overweight to obese participants with hypercholesterinemia.

3.4.1. Inclusion Criteria

Participants meeting all the following criteria will be eligible to participate in this trial:

1) Have given written informed consent

2) Males or females aged 18 to 70 years old at the time of first dosing

3) Satisfy the following:

- Females: Non-pregnant and non-lactating; documented surgically sterile, confirmed post-menopausal, or abstinent; or if engaged in sexual relations of childbearing potential, participant agrees to use two acceptable methods of contraception for 4 weeks prior to the treatment period, for the 4 weeks of the Treatment Period, and for at least 2 weeks after the last dose of study drug. One of the methods must be an appropriate hormonal contraceptive (stable for at least 4 weeks prior to treatment), and the other method can be an acceptable method of barrier contraception, e.g., a condom for the male partner.

- Males: Surgically sterile or abstinent; or if engaged in sexual relations of childbearing potential, the participant and his partner must agree to use an acceptable contraceptive method during the 4 weeks of the Treatment Period and for 2 weeks after the last dose of study drug.

4) Have a body mass index (BMI) of >25.0 and ≤ 45.0 kg/m2 at Screening

5) Have a documented history of dyslipidemia defined as LDL-C ≥ 2.59 mmol/L

3.4.2. Exclusion Criteria

1) Participants meeting any of the following criteria will be excluded from this trial:

2) The use of any anti-dyslipidemia agent within 28 days prior to dosing

3) History of a total cholesterol ≥ 10.35 mmol/L or triglyceride ≥ 11.3 mmol/L

4) History of a clinically significant cardiac arrhythmia or clinically significant abnormal ECG results at Screening

5) Significant peripheral or coronary vascular disease

6) Clinically significant abnormal blood pressure at Screening, defined as supine blood pressure ≥160/100 or < 90/60 mmHg.

7) Primary hypothyroidism (thyroid stimulating hormone [TSH] > upper limit or normal [ULN] and free T4 < lower limit of normal [LLN]), primary subclinical hypothyroidism (screening TSH > ULN and free T4 within normal limits [WNL]), or secondary hypothyroidism (screening TSH < LLN and free T4< LLN) at Screening.

8) Glucose-6-phosphate dehydrogenase (G6PD) deficiency

9) History of unstable proliferative retinopathy or maculopathy and/or severe neuropathy, in particular autonomic neuropathy, as judged by the Investigator.

10) Known history of, or positive test for, human immunodeficiency virus (HIV), hepatitis C, or chronic hepatitis B

11) Active infection that is currently producing symptoms or in which the causative organism of the disease is rapidly reproducing

12) Current or recent history (verbal report) in last 6 months of drug or alcohol abuse, or consumption of more than 30 g of alcohol (3 standard drinks) per day (for male and female participants) within 4 weeks prior to Screening, or positive urine drug screen for drugs of abuse

13) Clinically significant abnormalities identified during physical examination or from the participant's medical history such as:

    a. Any history of cardiac insufficiency defined as New York Heart Association (NYHA) Class II to IV

    b. Angina pectoris within the last 6 months

    c. Acute myocardial infarction at any time

    d. Major surgery within the last 3 months

    e. Stroke

14) Treatment with any agent that decreases body weight, actively enrolled in a weight loss program or following a special diet

15) Gastrointestinal conditions that involve malabsorption or inflammation (e.g., ulcerative

colitis, Crohn's disease), and recent or past bariatric surgery of any kind

16) Current or recent use of prohibited medications including (Section 4.4)

17) Current outpatient insulin use, or history of outpatient insulin use for more than 2 weeks in the last year.

18) Whole blood donation or significant blood loss within 30 days prior to screening or Plasma donation within 14 days prior to the first study drug administration.

19) User of any nicotine containing products within the past 6 months.

20) Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator.

21) Participation in an investigational drug trial within 30 days prior to dosing or 10 half-lives within the last dose of said investigational drug, whichever is longer.

22) The presence of any other conditions, which, in the opinion of the Investigator would make the participant unsuitable for inclusion, or could interfere with the participant participating in or completing the trial.

3.5. DETERMINATION OF SAMPLE SIZE

The sample size of 16 participants per cohort, with 12 receiving HTD1801 and 4 receiving placebo, was empirically determined and consistent with typical sample sizes used for similar studies to assess robust data for safety and PK.

3.6. TREATMENT ASSIGNMENT

There are three planned dose escalation cohorts. Each cohort will consist of 16 participants randomized 3:1 to receive either HTD1801 or placebo. The cohorts will be enrolled sequentially, but may overlap (the next cohort can begin during the Follow-up Period of the prior cohort). The decision to move to the next dose level will be based on safety findings and will not be dependent on establishing preliminary efficacy findings. Placebos will be pooled across cohorts to allow comparisons of each active dose vs placebo.

3.7. ADMINISTRATION OF STUDY MEDICATION

Study drug should be administered orally, once per day immediately following the morning meal on Day 1, twice per day following the morning and evening meals on Days 2 to 27 inclusive, and once per day immediately following the morning meal on Day 28. All study drug should be taken with a 240 mL of water (no more).

This trial includes three planned dose escalation cohorts. The doses of HTD1801 to be administered are summarized below in Table 1. The data will be analyzed for each active dose as

well as for pooled placebos with comparisons compared against pooled placebo and within each active dose group and pooled placebo.

Table 1. Planned Dose Escalation Cohorts

Cohort Number	Number of Participants Planned	Dose Regimen
1	12	HTD1801: 500 mg/day (250 mg bid)
	4	Placebo: 2 tablets/day (1 tablet bid)
2	12	HTD1801: 1000 mg/day (500 mg bid)
	4	Placebo: 4 tablets/day (2 tablets bid)
3	12	HTD1801: 2000 mg/day (1000 mg bid)
	4	Placebo: 8 tablets/day (4 tablets bid)

4. ANALYSIS POPULATIONS

All analysis populations will be defined and confirmed prior to database lock.

4.1. RANDOMIZED POPULATION

The Randomized Population will include all subjects randomized. Unless specified otherwise, this Population will be used for summaries and listings of subject disposition.

4.2. SAFETY POPULATION

The Safety Population will include all participants who received at least one dose of study drug or placebo. Subjects will be analyzed according to treatment received. The Safety Population will be used for subject listings unless otherwise stated and all analyses of safety.

4.3. EFFICACY POPULATION

The Efficacy Population will include all participants who received at least one dose of study drug or placebo, and had at least one post-dose assessment for the various secondary PD endpoints outlined in Section 8. Subjects will be analyzed according to treatment received. The Efficacy Population will be used for all analyses of PD endpoints.

4.4. PHARMACOKINETIC POPULATION

The Pharmacokinetic (PK) Population will include all participants who received active drug (HTD1801) and have sufficient data to calculate the PK parameters for UDCA and/or BBR.

4.5. PROTOCOL DEVIATIONS

No subject will be removed from analysis populations because of a protocol deviation.

5. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

5.1. GENERAL METHODS

Statistical methodology and analyses are in accordance with the principles outlined by the International Conference on Harmonization (ICH) E9 guidelines[1]. All statistical analyses will be done using SAS statistical software version 9.4 or higher.

The dictionary (MedDRA and WHODrug) version used will be specified in corresponding data display footnote.

Unless otherwise stated, all listings will include all subjects in Safety population, and all listings will be sorted by subject ID and assessment date/time.

Tabular summaries of data will be descriptive in nature (i.e., number of subjects [n], mean (arithmetic or geometric when appropriate), SD, median, minimum, and maximum for continuous variables and n and percent for categorical variables). Data from all cohorts will be summarized by treatment group in the order: Placebo, HTD1801 500 mg, HTD1801 1000 mg and HTD1801 2000 mg.

To help stabilize the variability for each laboratory parameter, the screening and baseline values will be averaged per subject in all calculations of mean change and mean percent change from averaged screening and baseline to Days 14 and 28.

For all percentage calculations, the denominator will be the number of subjects in the relevant population, unless otherwise stated.

Only data from protocol scheduled visits will be included in the summary tables. Data from unscheduled visits will not be included in the summary tables but will be included in the listings. All AE/SAE data will be included in the summary tables and respective listings.

Unless otherwise stated, baseline values defined in Section 5.2 will be used in summary tables. However, data collected at both the Screening visit and the Baseline visit will used in the listings.

No formal hypothesis testing will be performed in this Phase I study.

5.2. KEY DEFINITIONS

- Averaged Screening and Baseline Value: unless otherwise defined, the averaged screening and baseline value per subject will be used in all calculations of the change and percent change calculations; in the event that either screening or baseline value are missing, then the last available, valid, non-missing assessment prior to first dosing will serve as the averaged screening and baseline value.

Unknown, Not Done, Not Applicable and other classifications of missing data will not be considered when calculating baseline observations. However, valid categorical observations will be considered for baseline calculations.

- Study day: number of days since the study drug administration, which is counted as Day 1. Study day is calculated using the formula below:

  Study day = date of assessment - date of first dosing + 1, when date of assessment is on or after date of first dosing;

  Study day = date of assessment - date of first dosing, when date of assessment is before date of first dosing.

5.3. MISSING DATA

For each endpoint, in the event of missing Day 14 data, then the Baseline value will be carried forward; if the Baseline value is missing, then the Screening value will be carried forward. In the event of missing Day 28 data, then the Day 14 value will be carried forward; if the Day 14 value is missing, then the Baseline value will be carried forward.

Adverse events with partial/missing start date will be attributed to treatment emergent adverse event TEAE (Section 7.3 for definition of TEAE) based on imputed start date. Likewise, Medications with partial stop date will be attributed to prior or concomitant medications based on imputed stop date. However, start/stop date without imputation will be presented in listings.

1) Imputation for partial/missing start date of an adverse event:

- Completely missing, the earlier of stop date and first dosing;
- Only year reported, the earlier of stop date and last day of reported year;
- Only year and month reported, the earlier of stop date and last day of reported year and month.

2) Imputation for partial stop date of a medication:

- Only year reported, the last day of reported year;
- Only year and month reported, last day of reported year and month.

5.4. VISIT WINDOWS

No visit windows will be applied to any data.

6. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

6.1. SUBJECT DISPOSITION AND WITHDRAWALS

Subject disposition will be summarized and listed for Randomized population.

The number and percentage of subjects in each population, completed and discontinued the study, together with the reasons for discontinuation (withdrew consent, adverse event, protocol violation, lost to follow-up, investigator decision, pregnancy, study discontinued by sponsor, and other) will be presented.

6.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and baseline characteristics will be summarized and listed for Safety population.

Demographic data including age (years), sex (male, female), child bearing potential (yes, no), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, other), ethnicity (Hispanic or Latino, Not Hispanic or Latino) collected at study Screening will be summarized descriptively. Likewise, baseline characteristics including height (cm) and weight (kg) will also be summarized.

6.3. MEDICAL HISTORY

Medical history and physical exam findings will be coded with Medical Dictionary for Regulatory Activities (MedDRA) dictionary and summarized by system organ class (SOC) and preferred term (PT) based on the Safety population.

Subject listing of medical history will be provided.

6.4. OTHER BASELINE CHARACTERISTICS

The following baseline characteristics will be listed only.

- Diagnostics including Glucose-6-Phosphate Dehydrogenase (G6PD), Thyroid-Stimulating Hormone (TSH) and free T4 collected at Screening;
- Virology test including Human Immunodeficiency Virus (HIV), hepatitis B and C collected at Screening.

6.5. MEDICATION

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug). Prior and concomitant medications will be listed for Safety population with the classification (prior and/or concomitant) identified.

6.5.1. Prior Medication

All medications stopped before first dosing will be considered as prior medications. In case of a medication with partial stop date, imputation rule outlined in Section 5.3 will be applied.

Prior medications will only be included in data listings.

6.5.2. Concomitant Medication

All medications stopped on or after first dosing will be considered as concomitant medications. Medications with missing stop date will be considered as concomitant medication. In case of a medication with partial stop date, imputation rule outlined in Section 5.3 will be used.

Concomitant medications will be summarized by cohort, treatment, Anatomical Therapeutic Chemical (ATC) class and preferred term for all subjects in the Safety Set. Subjects who take the same medication (in terms of the preferred term) more than once will only be counted once for that medication.

7. SAFETY

Safety population will be used for all safety analysis. Safety will be assessed on the basis of adverse events, clinical laboratory, and vital signs.

7.1. EXTENT OF EXPOSURE

Extent of exposure will be summarized descriptively as a continuous variable. The CRF will capture the date of first dosing on Day 1 and the end date of last dosing. The extent of exposure (days) will be calculated as date of last dosing – date of first dosing + 1.

7.2. TREATMENT COMPLIANCE

Treatment compliance is defined as number of tablets taken/planned number of tablets. Number of tablets dispensed and returned will be recorded in CRF. Number of tablets taken will be calculated as number of tablets dispensed – number of tablets returned. Number of tablets planned will be calculated as number of exposure days * planned daily tables (2 tablets).

Treatment compliance as well as number of tablets dispensed, returned, and taken will be summarized descriptively as continuous variables.

7.3. ADVERSE EVENTS

Adverse Events (AEs) will be coded with Medical Dictionary for Regulatory Activities (MedDRA) and grouped by system organ class (SOC) and preferred term (PT).

AEs will be displayed for each active dose group and pooled placebo.

All AE summaries will be restricted to Treatment Emergent Adverse Events (TEAEs) only, but all AEs will be included in data listings. TEAEs are defined as any AE that commence on or after exposure to study drug or any pre-existing AE that worsens in either intensity or frequency after exposure to study drug. AE that worsened in either intensity or frequency will be recorded as a new AE in eCRF. In case of AE with partial/missing start date, data imputation rule outlined in Section 5.3 will be applied.

Drug-related TEAEs are defined as TEAEs with possible or probable relationship to study drug.

The number and percentage of subjects as well as number of events will be presented for TEAE summaries. For summaries by SOC and PT, a subject will be counted once at the SOC level and once at each PT within the SOC level. For summaries by SOC, PT, and severity, a subject will be counted once at each severity level for which the event occurred at the SOC level and at each severity level for which the event occurred for each unique PT within that SOC level. Summaries by relationship to study drug will be handled similar to the summaries by severity.

The following summaries will be provided.

- An overall summary of TEAEs presenting the number and percentage of subjects reporting TEAEs, serious TEAEs, severe TEAEs, drug-related TEAEs, TEAEs leading to withdrawal.
- TEAEs by SOC and PT
- TEAEs by SOC, PT and severity
- TEAEs by SOC, PT and relationship to study drug
- Serious TEAEs by SOC and PT

All AEs will be listed with TEAE identified. In addition, drug-related AEs, SAEs, and AEs leading to treatment interrupted or discontinued will be listed separately.

7.4. LABORATORY EVALUATIONS

Laboratory data including hematology, clinical chemistry, and urinalysis will be summarized descriptively at each protocol scheduled visit (Screening, Baseline, Day 14, Day 28), by cohort and treatment, as absolute values and changes from baseline. Baseline values will be determined as outlined in Section 5.2.

Low, normal, and high classifications will be applied to determine whether the laboratory test value was below (low), within (normal), or above (high) its reference range. Shifts from baseline in Low/normal/high classification for each parameter will be summarized by treatment group.

Each active dose will be compared to pooled placebo cohorts using an unpaired t-test while changes from baseline within each treatment group will be compared using a paired t-test.

Subject listing of laboratory evaluations will be provided.

8. ANALYSIS OF PHARMACODYNAMICS

Efficacy population will be used for all pharmacodynamics analysis. Pharmacodynamics will be assessed on the basis of lipid metabolism, glucose metabolism, and markers of liver function.

8.1. LIPID METABOLISM

Fasting lipid metabolism and atherogenic biomarkers will be assessed at Screening, Baseline, Day 14 and Day 28. Summary statistics for actual values, absolute changes from averaged screening and baseline, and percent changes from averaged screening and baseline will be tabulated by cohort and treatment. The averaged Screening and Baseline value will be determined as outlined in Section 5.2.

- Low-density lipoprotein-C (LDL-C)
- Non-high-density lipoprotein-C (non-HDL-C)
- Total cholesterol (TC), HDL-C, and TC/HDL-C ratio
- Apolipoprotein B (ApoB) and A-1 (ApoA1)
- Triglycerides and non-esterified fatty acid (NEFA)
- Serum proprotein convertase subtilisin/kexin type 9 (PCSK9)
- C- reactive protein (CRP) measured using a high-sensitivity assay
- Lipoprotein(a) [Lp(a)]

Column graph of mean and median change from baseline (absolute value and percentage) will be presented by dose group.

Each active dose will be compared to pooled placebo cohorts using an unpaired t-test while changes from baseline within each treatment group will be compared using a paired t-test.

8.2. GLUCOSE METABOLISM

Fasting glucose markers will be assessed at Screening, Baseline, Day 14 and Day 28. Summary statistics for actual values, absolute changes from averaged screening and baseline, and percent changes from averaged screening and baseline will be tabulated by cohort and treatment. The averaged Screening and Baseline value will be determined as outlined in Section 5.2.

- Glycosylated hemoglobin (HbA1c) level
- Fasting plasma glucose (FPG)

- Fasting serum insulin
- C-peptide

Column graph of mean and median change from baseline (absolute value and percentage) will be presented by dose group.

Each active dose will be compared to pooled placebo cohorts using an unpaired t-test while changes from baseline within each treatment group will be compared using a paired t-test.

8.3. MARKERS OF LIVER FUNCTION

Markers of liver function including alanine aminotransferase (ALT) and aspartate aminotransferase (AST) assessed at Screening, Baseline, Day 14 and Day 28. Summary statistics for actual values, absolute changes from averaged screening and baseline, and percent changes from averaged screening and baseline will be tabulated by cohort and treatment. The averaged Screening and Baseline value will be determined as outlined in Section 5.2.

Column graph of mean and median change from baseline (absolute value and percentage) will be presented by dose group.

Each active dose will be compared to pooled placebo cohorts using an unpaired t-test while changes from baseline within each treatment group will be compared using a paired t-test.

9. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

1. Section 4.3, the Efficacy Population will include all participants who received at least one dose of study drug or placebo, and had at least one post-dose assessment for the various secondary **PD** endpoints. Secondary PK endpoints will not be considered when determining Efficacy Population.

2. Section 5.2 redefines the Baseline to be the averaged Screening and Baseline in order to help stabilize the variance for each safety endpoint in computing mean change and mean percent change from averaged Screening and Baseline vs just Baseline. The mean change from averaged Screening and Baseline is also provided for each safety endpoint.

3. A carry forward algorithm is used to impute any missing Day 14 or 28 data. This is intended to be a conservative imputation strategy.

4. The following tables will be split in two as follows:

   14.2.1.1 – lipid metabolism (secondary endpoint/ efficacy population)

   - the value and the change from averaged screening and baseline
   - the % change from averaged screening and baseline

   14.2.2.1 – glucose metabolism (secondary endpoint/ efficacy population)

   - the value and the change from averaged screening and baseline
   - the % change from averaged screening and baseline

   14.2.3.1 – liver function (secondary endpoint/ efficacy population)

   - the value and the change from averaged screening and baseline
   - the % change from averaged screening and baseline

   14.3.4.1.1 – haematology (safety population)

   - the value and the change from averaged screening and baseline
   - the % change from averaged screening and baseline

   14.3.4.1.2 – serum chemistry (safety population)

   - the value and the change from averaged screening and baseline
   - the % change from averaged screening and baseline

   14.3.4.1.3 – urinalysis (safety population)

- the value and the change from averaged screening and baseline
- the % change from averaged screening and baseline

5. Each active dose will be compared to pooled placebo cohorts using an unpaired t-test while changes from baseline within each treatment group will be compared using a paired t-test.

10. REFERENCE LIST

1. ICH Guidance “E9 Statistical Principles for Clinical Trials.

11. PROGRAMMING CONSIDERATIONS

All tables, data listings, figures (TLFs), and statistical analyses will be generated using SAS® for Windows, Release 9.4 or higher (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

11.1. GENERAL CONSIDERATIONS

- One SAS program can create several outputs.
- Each output will be stored in a separate file.
- Output files will be delivered in RTF format.
- Numbering of TFLs will follow ICH E3 guidance.

11.2. TABLE, LISTING, AND FIGURE FORMAT

11.2.1. General

- All TLFs will be produced using the Courier New font, size 8
- The data displays for all TLFs will have a minimum 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

11.2.2. Tables

- The following tables will be produced:
    - 14.2.1.1 – lipid metabolism (secondary endpoint/ efficacy population)
    - 14.2.2.1 – glucose metabolism (secondary endpoint/ efficacy population)
    - 14.2.3.1 – liver function (secondary endpoint/ efficacy population)
    - 14.3.4.1.1 – haematology (safety population)
    - 14.3.4.1.2 – serum chemistry (safety population)

- 14.3.4.1.3 – urinalysis (safety population)

- For each of the above six sets of tables, the following will be produced:
  - the value and the change from averaged screening and baseline
  - the % change from averaged screening and baseline

- The following statistical tests will be performed for each of the above six sets of tables:
  - Unpaired t-tests will be used to compare each active dose vs. pooled placebos at each post-baseline time.
  - Paired t-tests will be used to compare on-study times vs pooled baseline (average of screening and baseline).

11.2.3. Headers

- All output should have the following header at the top left of each page:

  <Sponsor Name> Protocol XXX

  Draft/Final Run

- All output should have Page n of N at the top or bottom right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

11.2.4. Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended but sponsor preferences should be obtained prior to final determination (see also template 03.007C "Table of Contents for Tables Listings and Figures in Statistical Analysis Plan"). A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers.

- There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
Safety Population

11.2.5. Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- For numeric variables, include "unit" in column or row heading when appropriate.
- Analysis population sizes will be presented for each treatment group in the column heading as (N=xx). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set.
- The order of treatments in the tables and listings will be Placebo first.

11.2.6. Body of the Data Display

11.2.6.1. General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are right-justified; and
- numbers containing fractional portions are decimal aligned.

11.2.6.2. Table Conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

  Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).
- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.
- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.

- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

n	Xx
Mean (SD)	xx.x (xx.xx)
Median	xx.x
Min, Max	xx, xx

- P-values should be output in the format: "0.xxx", where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value should be less than 0.0001 then present as <0.0001. If the p-value is returned as >0.999 then present as >0.999
- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as 100%, without any decimal places.
- Tabular display of data for medical history, prior / concomitant medications, and all tabular displays of adverse event data should be presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) should be displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated should be reported as "-".
- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.
- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.
- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

11.2.6.3. Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.
- Missing data should be represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.
- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

11.2.7. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Subject specific footnotes should be avoided, where possible.
- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., 'Program : myprogram.sas').

12. QUALITY CONTROL

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. Syneos Health SOP 03.010 and 03.013 provide an overview of the development of such SAS programs.

Syneos Health SOP 03.009 describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

13. APPENDICES

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