Statistical Analysis Plan

Written by Datapharm Australia Pty. Ltd.

Prepared for

IMMURON LIMITED

Protocol Number: IMM-124E-2001

A phase II, randomized, double-blind, placebo-controlled dosing study of IMM-124E (bovine colostrum) for patients with non-alcoholic steatohepatitis (NASH)

SAP Version: FINAL

28 November 2017

Statistical Analysis Plan Approval Page

Study Title:	A phase II, randomized, double-blind, placebo-controlled dosing study of IMM-124E (bovine colostrum) for patients with non-alcoholic steatohepatitis (NASH)
Protocol Number:	IMM-124E-2001 (Version 1.3, 8 May 2016)

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The undersigned have reviewed this document and agree with the analysis to be performed on the data originating from the study protocol identified above.

Dr. Dan Peres Senior Head of Medical Immuron Limited	29 November 2017 Date
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1. ABBREVIATIONS

Abbreviation/term	Definition
Adj	Adjusted
BMI	Body mass index
ECG	Electrocardiogram
ET	Early Termination population
ETEC	Enterotoxic *Escherichia coli*
FAS	Full Analysis Set population
ITT	Intention to Treat population
ICH	International Conference on Harmonisation
HDL	Low High-density Lipoprotein
HFF	Hepatic fat fraction
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
LPS	Lipopolysaccharides
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Affairs
Min	Minimum
MRI	Magnetic resonance imaging
n	Number of observations
NAFL	Non-alcoholic fatty liver
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
PP	Per protocol population
Prob	Probability
SD	Standard deviation
SOC	System Organ Class
WHO DD	World Health Organisation Drug Dictionary

2. INTRODUCTION, STUDY DESIGN AND OBJECTIVES

2.1 Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in most of the Western world. Approximately 7.9% of the population in the United States has persistently elevated liver enzymes without any clear aetiology and it is hypothesized that over 80% of these cases are due to NAFLD. In those who have concomitant features of metabolic syndrome, the likelihood of NAFLD exceeds 90%. Based on Magnetic Resonance Imaging (MRI), it has been estimated that the overall prevalence of NAFLD in the United States is approximately 30%.

NAFLD is the hepatic manifestation of the metabolic syndrome, a condition characterized by the presence of at least three of five co-morbidities: abdominal (central) obesity, elevated blood pressure, elevated fasting plasma glucose, high serum triglycerides and low high-density lipoprotein (HDL) levels.

The probability of having NAFLD rises with increasing body mass index (BMI) with over 80% of subjects with a BMI > 35 having NAFLD. The histological spectrum of NAFLD includes: isolated hepatic steatosis, characterized by a fatty liver with no other histological abnormalities and also referred to as non-alcoholic fatty liver (NAFL); and steatohepatitis, characterized by steatosis associated with histological abnormalities that include cytological ballooning, Mallory's hyaline, inflammation and pericellular fibrosis. NASH is defined by the presence of predominantly macrovesicular hepatic steatosis or steatohepatitis in individuals who either do not consume alcohol or consume it in quantities that are not generally considered to be harmful to the liver. There are currently no non-invasive ways to distinguish NAFLD from NASH.

IMM-124E is hyperimmune bovine colostrum that is lactose- and fat-reduced. IMM-124E is harvested from the colostrum of dairy cows which have been immunized against the outer antigens, mostly lipopolysaccharides (LPS), of the most common strains of Enterotoxigenic *Escherichia coli* (ETEC). This inoculation activates a generalized immune response in the host animal to produce antibody clones which recognize and bind with the bacterial cell-surface epitopes presented. These polyclonal antibodies can also cross-react with other similar bacterial cell surface antigens.

IMM-124E has strong binding and neutralising activity against a wide range of LPS antigens. It is hypothesised that IMM-124E anti-LPS activity decreases the challenge of LPS to the liver and down-regulates the key T regulatory cell population associated with chronic inflammation and other metabolic defects associated with NASH.

In addition to its potential effect on bacterial translocation, IMM-124E contains adjuvants which promote regulatory T cells that suppress inflammation in target organs. The dual function of this product may be synergistic in alleviating NASH.

A clear unmet medical need remains in the treatment of NASH and an oral, well tolerated treatment for this condition is needed. Bovine colostrum, either as standard or hyperimmune colostrum, has an excellent safety profile

2.2 Study design

This was to be a randomized, double blind, placebo controlled, 3-arm parallel group, multi-dose, multi-centre study. The three treatment arms include 600mg IMM-124E three times daily, 1200mg IMM-124E three times daily and matching placebo. A total of 120 subjects, randomised to the three treatment groups in 1:1:1 ratio, having been previously diagnosed with NASH will be studied during a 24 week treatment period.

An interim analysis will be planned for this study, the purpose of which will be to determine whether any safety concerns exist as well as identify any preliminary signals for efficacy through examination of the primary, secondary and exploratory endpoints. The interim analysis will occur when 80 subjects have completed the 24 weeks treatment period and have both Baseline and 24 weeks' evaluable MRI hepatic fat fraction values. Each IMM-124E dose group will be compared to the placebo treatment group using pairwise contrasts. This analysis will occur for each of the hepatic fat fraction strata because of a differential response pattern across strata that have been noticed in previous studies on NASH (Le et al., 2012; Loomba et al., 2015).

2.3 Study objectives

The primary objectives of this study are to:

- Evaluate the safety and preliminary efficacy of two dose levels of IMM-124E in reducing liver fat compared with placebo in subjects with biopsy proven NASH.

The secondary objectives are to:

- Determine the pharmacokinetic profile of IMM-124E.
- Assess the impact of treatment with IMM-124E on markers of glucose metabolism and serum lipid profile.
- Assess the impact of treatment on liver function over 24 weeks.
- Establish the recommended dose.

Exploratory objectives are to investigate the impact of treatment on potentially relevant immune and metabolic biomarkers associated with NASH.

3. ANALYSIS POPULATIONS AND GENERAL STATISTICAL METHODOLOGY

This analysis plan is based on version 1.3 of the protocol, dated 8 May 2016, and includes other changes discussed at a later date.

3.1 Analysis populations

The Safety population will consist of all subjects who received at least one dose of study drug. All safety analyses will be analysed based on the treatment actually received. A subset of the safety population will be the Early Termination (ET) population. The ET population will consist of all subjects who withdrew after being randomised but before completing the Week 24 visit.

The Intention-to-Treat (ITT) population will consist of all subjects who were randomised, regardless of whether they received study drug or not. This population will be tested only if at least one subject was randomised but did not receive any study drug. All efficacy analyses will be based on the treatment to which each subject was randomised.

Full Analysis Set (FAS) for efficacy includes all subjects who received at least one dose of study medication. Only subjects with clear documentation that no study medication was received may be excluded. In the event of treatment allocation errors, subjects will be analysed for efficacy according to the treatment to which they were randomised. The FAS population will consist of the same set of patients as the Safety population. The only difference between the Safety and FAS populations will be the treatment group patients are analysed in, if any misallocation of treatment occurs.

The per protocol (PP) population will consist of all subjects who were randomised, completed the entire 24 week treatment period, were at least 85% - 115% compliant with the study drug, had liver MRIs at baseline and Week 24 and had no major protocol violations. Major protocol violations are deviations decided and documented prior to data lock and un-blinding of the randomisation code presumed by the medical monitor of having significant potential to distort the results of the study such as where a patient has been given an incorrect dispense or where they failed to satisfy inclusion or exclusion criteria. The PP population will be analysed according to the group to which they were randomised.

3.2 Visit windows

For visits during the first four weeks of treatment, and visit window of $\pm$1 day will apply, whereas after four weeks of treatment and during the follow-up period, the visit window will be $\pm$3 days.

3.3 General statistical methodology

Treatment groups will be described as '600 mg IMM-124E', '1200 mg IMM-124E' and 'Placebo'. All tables, figures and listings will be produced for these three treatment groups. In addition, where specified, tables will be produced where subjects are grouped by baseline hepatic fat fraction, baseline HbA1c, and with a binary classification (not treated vs. treated).

General descriptive statistics for continuous measures will include number of observations (n), mean, standard deviation (SD), median, quartiles, minimum and maximum. For categorical variables, descriptive statistics will include n and percentage occurrence within the treatment group. The denominator for calculating percentage will be the number of valid observations within the treatment group.

For the basic and interim analysis, missing data will remain missing and not be imputed. However, for sensitivity measures in the final study analysis, missing values will also be imputed using a multiple imputation technique (Berglund, 2010 and Yuan, 2011).

This is a multicentre study, but no analysis using centre as a stratification factor will be performed, except for the primary endpoint, in which case the analysis will be performed on the imputed data both with and without centre as a stratification factor as a sensitivity analysis on the primary endpoint. Analysis of centre as a stratification factor will also be performed on ALT, AST, Glucose, A_1c, lipid profile parameters and CK-18.

Concomitant medications will be coded using the most recently available version of the World Health Organisation Drug Dictionary (WHO DD) at the time of data lock. Medications will be summarised and tabulated using the first and second levels of the dictionary. Medical history and adverse events will be coded using the most recently available version of the Medical Dictionary for Regulatory Affairs (MedDRA) at the time of data lock. Both medical history and adverse events will be summarised and tabulated using System Organ Class and Preferred Terms.

Patients given the wrong treatment will be analysed as randomised for efficacy measures (for the ITT, PP and FAS populations) and as treated for safety measures (Safety population and ET subgroup).

For safety data, if there are unscheduled visits where data values exist and those data are missing for the prior, scheduled, visit, then the values from the unscheduled visit will be imputed.

In the case of multiple occurrences of the same visit, the data from the latest visit date will be used if prior to the first dose. After the first dose, the data from the earliest visit date will be used. All data collected will be presented in the data listings.

All programming for statistical analysis, data listing and production of figures will be done in version 9.4 of SAS.

3.4 Data handling

Data collected during the course of this study have been entered into an IBM Clinical Development formerly known as eClinical OS (eCOS) electronic clinical record database, which is a commercially available database (Merge, now an IBM company) specifically designed for such use. Data is entered into the database at each study centre. SAS datasets are one of the outputs of the database. Following review, validation and correction of the data entered into the database, a meeting will be held to declare the file to be clean and proceed to data lock, after which no changes to the data are possible. At the Clean File meeting, analysis populations will be discussed and finalised. Following the signing of the Clean File document by all signatories, the randomisation code will be broken following Datapharm Australia standard operating procedures set for that activity.

4. SUBJECT DISPOSITION AND WITHDRAWAL

4.1 Subject disposition

Subject disposition will be presented in the form of a flow chart for the Clean File meeting which will be included in the study report. Information included in the flow chart will include the number of subjects enrolled, number available for each of the analysis populations (Safety, ET, ITT, FAS, PP) and reasons for those not available. The flow chart will include unblinded subject identification numbers. A summary table will be produced that provides counts and percentages of subjects in each analysis population and the reason for exclusion from subsequent analysis populations.

4.2 Study completion and withdrawal

A table will be produced that summarises the number of subjects enrolled, and number withdrawn by withdrawal reason.

5. DEMOGRAPHIC AND OTHER CHARACTERISTICS AT BASELINE

5.1 Demographic data

Demographic data collected at subject entry into the study, including age, gender, height, weight, BMI and race together with other characteristics recorded in the CRF at the Screening or Baseline visit will be summarised by descriptive statistics or frequency tabulations by treatment group. For the demographics and other data in this section, the FAS population will be used and grouped by treatment. Further tables will also be produced, which group the data by treatment, HFF and A1c levels.

5.2 Disease characteristics

Previous treatment regimens for NAFLD and NASH will be summarised by their current status and treatment group. Liver biopsy data collected prior to enrolment in the study will also be summarised, including fibrosis, inflammation, ballooning, and steatosis scores. Baseline clinical chemistry values such as ALT, AST and A_1c will also be presented. These characteristics may be used to subgroup populations in the primary analysis (as described in Section 7.2).

5.3 Medical history

Medical history entries will be coded using MedDRA. The data will be summarised and tabulated by SOC and Preferred Term as well as treatment group. The summary table will indicate resolved versus current events as collected in the eCRF.

5.4 Prior medications

Prior medications are those medications taken by subjects and ceased prior to entry into the study. These medications will be coded using WHO DD and will be summarised and tabulated by first and second level terms and treatment group.

5.5 Concomitant medications

Concomitant medications are those medications taken by subjects during the course of the study. These medications will be coded using WHO DD and will be summarised and tabulated by first and second level terms and treatment group. New medications are those drugs commenced during the study, and will be coded and presented in the same manner as concomitant medications.

5.6 Other data collected at Baseline

12-lead electrocardiographic values will be summarised and tabulated by treatment group. Summary tables for HbA1c and hepatic fat fraction, including number of subjects in each category will also be produced.

6. COMPLIANCE

Compliance is derived from the drug accountability data and is calculated as the percentage of study treatment to be received versus that was actually taken by the subject. A table of compliance by treatment group will be produced, whereby counts of subjects that were <50%, 50%-<85%, 85%-115%, and >115% will be displayed. In cases where bottles were not returned and drug counts are not available, compliance for that period will be estimated from the eCRF compliance assessment according to the rules set within the Clean File document.

7. EFFICACY ANALYSES

7.1 Primary efficacy assessments

The primary outcome for this study will be the mean change from Baseline in the percentage fat content (hepatic fat fraction) of the liver measured by Magnetic Resonance Imaging (MRI) at Week 24.

7.2 Primary efficacy analyses

The hepatic fat fraction will be summarised and tabulated for the Baseline and Week 24 visits along with change from Baseline by randomised treatment group. Change in hepatic fat fraction from Baseline will be analysed using analysis of variance on the ITT, PP and FAS populations, where the model will include the treatment group and another subgrouping variable. As determined by baseline values, hepatic fat fraction categories ($\leq$10%, >10% - <21%, $\geq$21% - <30% and $\geq$30%), HbA1c group (< 6% and $\geq$6%), and ALT (greater or less than 1.5 x the upper normal limit) will be used to subgroup the analysis populations. Further, data from liver biopsies up to 6 months prior to screening will also be used to subgroup analysis populations based on fibrosis (0-1 vs. 2-3), NAS inflammation (0-1 vs. 2-3), and NAS ballooning (0-1 vs. 2). These will be used in addition to the main effects factors and the two-way interaction of those main effects.

In the primary analysis, any missing data will remain missing. Treatment effects between placebo and each of the active treatment groups within each of the hepatic fat and HbA1c categories will be generated and tested for significant differences between treatment and placebo using pre-specified contrasts.

To examine the effect of treatment within the various levels of these subgroup variables, a mixed models ANOVA will be employed if there are an appropriate number of observations in each cell (created by the crossing of study treatment and subgroup categories) and the data does not differ significantly from a normal distribution. In the event that this is not the case, the data will be ranked in an attempt to normalise it, and pairwise contrasts between treatment groups will be performed using Wilcoxon rank sum tests within each combination of visit and subgroup variable level will be performed. However, if the ranked data is also not normally distributed, a permutation test will be employed whereby the unranked data will be randomly sampled (Lehmann, 2006). No adjustment for multiple testing will be made. See Appendix 1 for more information on both the Wilcoxon rank-sum test and the permutation test.

Sensitivity analyses will be performed in the final study analysis and will use the same analysis method on the FAS and PP populations using the multiple imputation and analysis method to impute missing values and, finally, an analysis using the full set of ITT population data, but including study centre as an additional main effect.

Interaction effects with study centre will not be investigated. If any outliers are detected (defined as greater than ± 2 SD away from the mean for that group and visit combination), sensitivity analyses will be performed where those outliers are removed and then will be compared with the analysis where those outliers were not taken out.

7.3 Secondary efficacy analyses

The following analyses of secondary efficacy will be performed on the FAS population. However, if the results for the primary efficacy analysis differ across populations, the ITT and PP populations may also be subject to secondary efficacy analysis. For the analyses detailed in this section and section 7.4, inferential statistical analysis will be performed on the same basis as for the primary endpoint. For those values that are recorded at 3 or more time-points, the baseline value will be included in the repeated measures analysis as a covariate. For analyses with only a baseline and final value, t-tests or Wilcoxon rank-sum tests will be performed depending on the distribution of the data. In addition to this, the mean change from baseline for all relevant variables will be assessed and presented.

Serum concentrations of IMM-214E bovine antibodies (including but not limited to: maximum and minimum observed concentration, area under the concentration-time curve, and (if feasible) elimination half-life) will be summarised and tabulated by visit and time point. Pharmacokinetic coefficients, including but not limited to, maximal and minimal concentration, area under the concentration curve and, if possible, elimination half-life will also be summarised and tabulated with change from Baseline by visit.

Body mass index (BMI), waist circumference and waist:hip ratio with change from Baseline will be summarised and tabulated by visit and treatment group.

HbA1c, glucose and homeostatic model assessment of insulin resistance (HOMA-IR) will be summarised and tabulated with change from Baseline by visit and treatment group.

Serum lipid profile values of total cholesterol, triglycerides and high and low density lipoproteins with change from Baseline and number of clinically significant values will be summarised and tabulated by visit and treatment group. Liver function values of ALT, AST, GGT, bilirubin and albumin, with change from Baseline will be summarised and tabulated by visit and treatment group. These liver function tests will also be correlated with HFF, CRP, and A1c. The proportion of subjects with ALT within the normal reference range at Week 24 will be summarised and tabulated by treatment group. Logistic regression modelling will be used to compare proportions in the Placebo group against each of the IMM-124E treatment dose groups using the same model used in the primary efficacy analysis, although the Baseline value of the liver function analyte will be used as a covariate. The area under the curve for change

from Baseline to Week 24, using the Baseline value as reference, for liver enzymes ALT, AST and GGT will also be analysed. For patients in the FAS population who withdraw prior to Week 24, the area under the curve will be adjusted in a manner comparable to a full 24 week period value.

The proportion of subjects demonstrating a decrease in liver percent fat at 24 weeks compared to baseline of 5%, 10%, 20% and 30% respectively will also be analysed. In a similar manner, proportional decreases in ALT, AST and A1c will be assessed using appropriate percentages.

Correlations between change in hepatic fat fraction and changes in ALT, C-reactive protein and A_1c will also be calculated.

The Fibrosis-4 Score will be calculated at each visit for which there is data. The formula is FIB-4 = (Age * AST) / (Platelets / SQRT(ALT)). This score will be summarised and tabulated in the same manner as the primary endpoint.

7.4 Exploratory efficacy analyses

Biomarkers, lipopolysaccharides (LPS), C-reactive protein, cytokeratin-18 fragments, C-reactive protein, PBMCs and numerous other compounds will be summarised with change from Baseline and tabulated by visit and treatment group in order to assess the effect of the treatment on the innate immunity of the body.

Serum metabolomics and gut microbiome are indicated in the protocol as being exploratory endpoints, but no additional detail was provided. Any additional analysis will be explained in full in the final study report.

Regulatory T cells will be summarised with change from Baseline and tabulated by visit and treatment group.

The gut microbiome will also be characterised by study treatment and Baseline hepatic fat fraction category in order to assess the effect of the treatment on the adaptive immunity of the body. This analysis may be performed by a different supplier.

Some endpoints will be explored for dose effects, and further ad-hoc analyses may be performed as required by the sponsor or regulatory bodies.

8. SAFETY ANALYSES

8.1 Exposure to study treatments

Exposure to study treatments will be calculated as date of last treatment minus date of start of treatment + 1. If unknown, date of last treatment will be estimated and imputed. Exposure will be summarised using descriptive statistics and tabulated by treatment group. For this and the other safety analyses described in this section, the populations displayed will be the Safety population and ET sub-group.

8.2 Adverse events

Adverse events will be coded by MedDRA SOC and Preferred Term, and summarised and tabulated for the safety population. For each Preferred Term the number and percent of subjects reporting each adverse event will be tabulated by treatment group. These tables include:

- Adverse event summary table
- Adverse events occurring prior to study treatment, if any
- All treatment-emergent adverse events
- Most common (>5%) treatment-emergent adverse events in any group
- Treatment emergent adverse events that were possibly, probably or definitely related to the study medication (if large study then only the most common of these may be presented in Section 12 tables)
- Severe adverse events
- Adverse events causing withdrawal
- All adverse events by maximum severity and relationship to study treatment, with subject identification. (ICH format)

Odds ratios will be calculated for the 15 most commonly reported Preferred Terms.

8.3 Serious adverse events

Serious adverse events will be tabulated in the same way as all adverse events. In addition, anecdotal descriptions of each serious adverse event will be provided.

8.4 Vital signs

Vital signs, including resting pulse, systolic and diastolic blood pressures, respiratory rate, and body temperature will be summarised with change from Baseline and tabulated by visit and treatment group.

8.5 Laboratory safety measurements

Serum biochemistry parameters will be summarised with change from Baseline and the count of clinically significant values and tabulated by visit. If multiple units are reported in the eCRF, values will be transformed to SI units prior to summary. Additionally, a serum biochemistry shift table, showing the number of normal values, abnormal (both above and below normal range) but not clinically significant, clinically significant (both above and below normal range) at Baseline and each visit during the treatment and follow-up periods will also be produced. Parameters summarised and tabulated in lipid panel, biomarkers and regulatory T cell tables will be excluded.

Haematology parameters will be summarised with change from Baseline and the count of clinically significant values and tabulated by visit. Additionally, a haematology shift table, showing the number of normal values, abnormal (both above and below normal range) but not clinically significant clinically significant (both above and below normal range) at Baseline and each visit during the treatment and follow-up periods will also be produced.

8.6 ET subgroup analysis

As defined in section 3.1, The ET population is a subset of the Safety population and as such will be grouped based on the study drug they took, rather than the group to which they were randomised. The data of the ET population will be analysed in order to determine the reasons for the withdrawal and will explore the last available ALT, HbA1c, and other assessment variables. The timing of the withdrawal will also be assessed in addition to a summary of baseline values for any similarities the population may share.

8.7 Other safety analyses

Physical examination results will be summarised using descriptive statistics with change from Baseline and tabulated by visit. At Screening, a full physical examination will be performed, but from Baseline through the follow-up period, a targeted physical examination will be performed.

9. INTERIM ANALYSES

An interim analysis is planned when 80 subjects have completed the full 24 week study period. The analysis population will include data from those 80 subjects up to and including week 24, in addition to all early terminations (up to and including week 24) and all remaining currently randomised subjects with post-baseline data prior to the 28th of February 2017. Populations in the interim analysis will use the same definitions as the full analysis at the end of the study.

The purpose of this interim analysis will be to establish the safety of the study treatment, identify signals of efficacy of the two dose groups (600mg and 1200mg) against Placebo and to set sample size parameters for potential future studies. As a result, the critical probability for the interim analysis will be 0.00305, which requires the final alpha level to be 0.04695. All populations will be analysed for the interim analysis as described above.

10. CHANGES FROM THE PROTOCOL

Any changes from version 1.3 of the protocol dated 8 May 2016 will be documented in the final study report.

11. REFERENCES

Berglund, P.A., An introduction to multiple imputation of complex sample data using SAS, Paper 265 – 2010, SAS Global Forum 2010.

Le TA, Chen J, Changchien C, Peterson MR, Kono Y, Patton H, Cohen BL, Brenner D, Sirlin C, Loomba R. Effect of colesevelam on liver fat quantified by magnetic resonance in nonalcoholic steatohepatitis: a randomized controlled trial. Hepatology. 2012 Sep 1;56(3):922-32.

Lehmann EL, D'Abrera HJ. Nonparametrics: statistical methods based on ranks. New York: Springer; 2006.

Loomba R, Sirlin CB, Ang B, Bettencourt R, Jain R, Salotti J, Soaft L, Hooker J, Kono Y, Bhatt A, Hernandez L. Ezetimibe for the treatment of nonalcoholic steatohepatitis: assessment by novel magnetic resonance imaging and magnetic resonance elastography in a randomized trial (MOZART trial). Hepatology. 2015 Apr 1;61(4):1239-50.

Yuan, Y. C., Multiple imputation for missing data: Concepts and new development (Version 9.0), Journal of Statistical Software, 45(6) Dec 2011.

12. TABLE AND FIGURE LISTINGS

Table Section	Table Title (Population)
Section 10.1	Subject disposition (usually from Clean File document)
Section 10.2	Protocol deviations (usually compiled by medical writers from listing)
Section 11.1	Analysis populations
Section 11.2	Demographics (FAS population)
	Prior Medical History events (FAS population)
	Current Medical History events (FAS population)
	Prior medications ceased before study treatment (FAS population)
	Concomitant medications taken during study (FAS population)
	New medications commenced after start of study treatment (FAS population)
	Histological results from liver biopsy prior to Screening (FAS population)
Section 11.3	Compliance (ITT, PP, FAS populations)
Section 11.4	Hepatic fat fraction (ITT population)
	Analysis of change in hepatic fat fraction (ITT population)
	Hepatic fat fraction (FAS population)
	Analysis of change in hepatic fat fraction (FAS population)
	Hepatic fat fraction (PP population)
	Analysis of change in hepatic fat fraction (PP population)
	Analysis of hepatic fat fraction using multiple imputation and analysis method (ITT population)
	Analysis of hepatic fat fraction using multiple imputation and analysis method (FAS population)
	Analysis of hepatic fat fraction with site as stratification factor (ITT population)
	Analysis of hepatic fat fraction with site as stratification factor (FAS population)
	Analysis of hepatic fat fraction with site as stratification factor (PP population)
	Hepatic fat fraction with Hepatic fat fraction sub-groups as stratification factor (ITT population)
	Hepatic fat fraction with Hepatic fat fraction sub-groups as stratification factor (FAS population)
	Hepatic fat fraction with Hepatic fat fraction sub-groups as stratification factor (PP population)
	Hepatic fat fraction with Fibrosis sub-groups as stratification factor (ITT population)
	Hepatic fat fraction with Fibrosis sub-groups as stratification factor (FAS population)
	Hepatic fat fraction with Fibrosis sub-groups as stratification factor (PP population)
	Hepatic fat fraction with Ballooning sub-groups as stratification factor (ITT population)
	Hepatic fat fraction with Ballooning sub-groups as stratification factor (FAS

population)

Hepatic fat fraction with Ballooning sub-groups as stratification factor (PP population)

Hepatic fat fraction with HbA1c sub-groups as stratification factor (ITT population)

Hepatic fat fraction with HbA1c sub-groups as stratification factor (FAS population)

Hepatic fat fraction with HbA1c sub-groups as stratification factor (PP population)

Hepatic fat fraction with Inflammation sub-groups as stratification factor (ITT population)

Hepatic fat fraction with Inflammation sub-groups as stratification factor (FAS population)

Hepatic fat fraction with Inflammation sub-groups as stratification factor (PP population)

Hepatic fat fraction with ALT sub-groups as stratification factor (ITT population)

Hepatic fat fraction with ALT sub-groups as stratification factor (FAS population)

Hepatic fat fraction with ALT sub-groups as stratification factor (PP population)

Hepatic fat fraction with outliers excluded (ITT population)

Hepatic fat fraction with outliers excluded (FAS population)

Hepatic fat fraction with outliers excluded (PP population)

ALT area under the curve values for 24 weeks of treatment (ITT population)

ALT area under the curve values for 24 weeks of treatment (FAS population)

ALT area under the curve values for 24 weeks of treatment (PP population)

ALT area under the curve values for 24 weeks of treatment with hepatic fat fraction sub-groups as stratification factor (ITT population)

ALT area under the curve values for 24 weeks of treatment with hepatic fat fraction sub-groups as stratification factor (FAS population)

ALT area under the curve values for 24 weeks of treatment with hepatic fat fraction sub-groups as stratification factor (PP population)

ALT area under the curve values for 24 weeks of treatment with HbA1c sub-groups as stratification factor (ITT population)

ALT area under the curve values for 24 weeks of treatment with HbA1c sub-groups as stratification factor (FAS population)

ALT area under the curve values for 24 weeks of treatment with HbA1c sub-groups as stratification factor (PP population)

ALT area under the curve values for 24 weeks of treatment with Fibrosis sub-groups as stratification factor (ITT population)

ALT area under the curve values for 24 weeks of treatment with Fibrosis sub-groups as stratification factor (FAS population)

ALT area under the curve values for 24 weeks of treatment with Fibrosis sub-groups as stratification factor (PP population)

ALT area under the curve values for 24 weeks of treatment with Ballooning sub-groups as stratification factor (ITT population)

ALT area under the curve values for 24 weeks of treatment with Ballooning sub-groups as stratification factor (FAS population)

ALT area under the curve values for 24 weeks of treatment with Ballooning sub-groups as stratification factor (PP population)

ALT area under the curve values for 24 weeks of treatment with Inflammation sub-groups as stratification factor (ITT population)

ALT area under the curve values for 24 weeks of treatment with Inflammation sub-groups as stratification factor (FAS population)

ALT area under the curve values for 24 weeks of treatment with Inflammation sub-groups as stratification factor (PP population)

ALT area under the curve values for 24 weeks of treatment with ALT sub-groups as stratification factor (ITT population)

ALT area under the curve values for 24 weeks of treatment with ALT sub-groups as stratification factor (FAS population)

ALT area under the curve values for 24 weeks of treatment with ALT sub-groups as stratification factor (PP population)

AST area under the curve values for 24 weeks of treatment (ITT population)

AST area under the curve values for 24 weeks of treatment (FAS population)

AST area under the curve values for 24 weeks of treatment (PP population)

AST area under the curve values for 24 weeks of treatment with hepatic fat fraction sub-groups as stratification factor (ITT population)

AST area under the curve values for 24 weeks of treatment with hepatic fat fraction sub-groups as stratification factor (FAS population)

AST area under the curve values for 24 weeks of treatment with hepatic fat fraction sub-groups as stratification factor (PP population)

AST area under the curve values for 24 weeks of treatment with HbA1c sub-groups as stratification factor (ITT population)

AST area under the curve values for 24 weeks of treatment with HbA1c sub-groups as stratification factor (FAS population)

AST area under the curve values for 24 weeks of treatment with HbA1c sub-groups as stratification factor (PP population)

AST area under the curve values for 24 weeks of treatment with Fibrosis sub-groups as stratification factor (ITT population)

AST area under the curve values for 24 weeks of treatment with Fibrosis sub-groups as stratification factor (FAS population)

AST area under the curve values for 24 weeks of treatment with Fibrosis sub-groups as stratification factor (PP population)

AST area under the curve values for 24 weeks of treatment with Ballooning sub-groups as stratification factor (ITT population)

AST area under the curve values for 24 weeks of treatment with Ballooning sub-groups as stratification factor (FAS population)

AST area under the curve values for 24 weeks of treatment with Ballooning sub-groups as stratification factor (PP population)

AST area under the curve values for 24 weeks of treatment with Inflammation sub-groups as stratification factor (ITT population)

AST area under the curve values for 24 weeks of treatment with Inflammation sub-groups as stratification factor (FAS population)

AST area under the curve values for 24 weeks of treatment with Inflammation sub-groups as stratification factor (PP population)

AST area under the curve values for 24 weeks of treatment with ALT sub-groups as stratification factor (ITT population)

AST area under the curve values for 24 weeks of treatment with ALT sub-groups as stratification factor (FAS population)

AST area under the curve values for 24 weeks of treatment with ALT sub-groups as stratification factor (PP population)

GGT area under the curve values for 24 weeks of treatment (ITT population)

GGT area under the curve values for 24 weeks of treatment (FAS population)

GGT area under the curve values for 24 weeks of treatment (PP population)

GGT area under the curve values for 24 weeks of treatment with hepatic fat fraction sub-groups as stratification factor (ITT population)

GGT area under the curve values for 24 weeks of treatment with hepatic fat fraction sub-groups as stratification factor (FAS population)

GGT area under the curve values for 24 weeks of treatment with hepatic fat fraction sub-groups as stratification factor (PP population)

GGT area under the curve values for 24 weeks of treatment with HbA1c sub-groups as stratification factor (ITT population)

GGT area under the curve values for 24 weeks of treatment with HbA1c sub-groups as stratification factor (FAS population)

GGT area under the curve values for 24 weeks of treatment with HbA1c sub-groups as stratification factor (PP population)

GGT area under the curve values for 24 weeks of treatment with Fibrosis sub-groups as stratification factor (ITT population)

GGT area under the curve values for 24 weeks of treatment with Fibrosis sub-groups as stratification factor (FAS population)

GGT area under the curve values for 24 weeks of treatment with Fibrosis sub-groups as stratification factor (PP population)

GGT area under the curve values for 24 weeks of treatment with Ballooning sub-groups as stratification factor (ITT population)

GGT area under the curve values for 24 weeks of treatment with Ballooning sub-groups as stratification factor (FAS population)

GGT area under the curve values for 24 weeks of treatment with Ballooning sub-groups as stratification factor (PP population)

GGT area under the curve values for 24 weeks of treatment with Inflammation sub-groups as stratification factor (ITT population)

GGT area under the curve values for 24 weeks of treatment with Inflammation sub-groups as stratification factor (FAS population)

GGT area under the curve values for 24 weeks of treatment with Inflammation sub-groups as stratification factor (PP population)

GGT area under the curve values for 24 weeks of treatment with ALT sub-groups as stratification factor (ITT population)

GGT area under the curve values for 24 weeks of treatment with ALT sub-groups as stratification factor (FAS population)

GGT area under the curve values for 24 weeks of treatment with ALT sub-groups as stratification factor (PP population)

Proportion of subjects with normal ALT by visit (FAS population)

Proportion of subjects with normal ALT by visit (ITT population)

Proportion of subjects with normal ALT by visit (PP population)

Proportion of subjects with normal ALT with Hepatic fat fraction sub-groups as stratification factor by visit (FAS population)

Proportion of subjects with normal ALT with Hepatic fat fraction sub-groups as stratification factor by visit (ITT population)

Proportion of subjects with normal ALT with Hepatic fat fraction sub-groups as stratification factor by visit (PP population)

Proportion of subjects with normal ALT with HbA1c sub-groups as stratification factor by visit (FAS population)

Proportion of subjects with normal ALT with HbA1c sub-groups as stratification factor by visit (ITT population)

Proportion of subjects with normal ALT with HbA1c sub-groups as stratification factor by visit (PP population)

Proportion of subjects with normal ALT with Fibrosis sub-groups as stratification factor by visit (FAS population)

Proportion of subjects with normal ALT with Fibrosis sub-groups as stratification factor by visit (ITT population)

Proportion of subjects with normal ALT with Fibrosis sub-groups as stratification factor by visit (PP population)

Proportion of subjects with normal ALT with Ballooning sub-groups as stratification factor by visit (FAS population)

Proportion of subjects with normal ALT with Ballooning sub-groups as stratification factor by visit (ITT population)

Proportion of subjects with normal ALT with Ballooning sub-groups as stratification factor by visit (PP population)

Proportion of subjects with normal ALT with Inflammation sub-groups as stratification factor by visit (FAS population)

Proportion of subjects with normal ALT with Inflammation sub-groups as stratification factor by visit (ITT population)

Proportion of subjects with normal ALT with Inflammation sub-groups as stratification factor by visit (PP population)

Proportion of subjects with normal ALT with ALT sub-groups as stratification factor by visit (FAS population)

Proportion of subjects with normal ALT with ALT sub-groups as stratification factor by visit (ITT population)

Proportion of subjects with normal ALT with ALT sub-groups as stratification factor by visit (PP population)

Proportion of subjects with 30% reduction in ALT by visit (FAS population)

Proportion of subjects with 30% reduction in ALT by visit (ITT population)

Proportion of subjects with 30% reduction in ALT by visit (PP population)

Proportion of subjects with 30% reduction in ALT with Hepatic fat fraction sub-groups as stratification factor by visit (FAS population)

Proportion of subjects with 30% reduction in ALT with Hepatic fat fraction sub-groups as stratification factor by visit (ITT population)

Proportion of subjects with 30% reduction in ALT with Hepatic fat fraction sub-groups as stratification factor by visit (PP population)

Proportion of subjects with 30% reduction in ALT with HbA1c sub-groups as stratification factor by visit (FAS population)

Proportion of subjects with 30% reduction in ALT with HbA1c sub-groups as stratification factor by visit (ITT population)

Proportion of subjects with 30% reduction in ALT with HbA1c sub-groups as stratification factor by visit (PP population)

Proportion of subjects with 30% reduction in ALT with Fibrosis sub-groups as stratification factor by visit (FAS population)

Proportion of subjects with 30% reduction in ALT with Fibrosis sub-groups as stratification factor by visit (ITT population)

Proportion of subjects with 30% reduction in ALT with Fibrosis sub-groups as stratification factor by visit (PP population)

Proportion of subjects with 30% reduction in ALT with Ballooning sub-groups as stratification factor by visit (FAS population)

Proportion of subjects with 30% reduction in ALT with Ballooning sub-groups as stratification factor by visit (ITT population)

Proportion of subjects with 30% reduction in ALT with Ballooning sub-groups as stratification factor by visit (PP population)

Proportion of subjects with 30% reduction in ALT with Inflammation sub-groups as stratification factor by visit (FAS population)

Proportion of subjects with 30% reduction in ALT with Inflammation sub-groups as stratification factor by visit (ITT population)

Proportion of subjects with 30% reduction in ALT with Inflammation sub-groups as stratification factor by visit (PP population)

Proportion of subjects with 30% reduction in ALT with ALT sub-groups as stratification factor by visit (FAS population)

Proportion of subjects with 30% reduction in ALT with ALT sub-groups as stratification factor by visit (ITT population)

Proportion of subjects with 30% reduction in ALT with ALT sub-groups as stratification factor by visit (PP population)

Glucose metabolism markers (A1c, HOMA-IR, glucose, insulin) by visit (FAS population)

Glucose metabolism markers (A1c, HOMA-IR, glucose, insulin) by visit (ITT populations)

Glucose metabolism markers (A1c, HOMA-IR, glucose, insulin) by visit (PP population)

Glucose metabolism markers (A1c, HOMA-IR, glucose, insulin) by visit with hepatic fat fraction sub-groups as stratification factor (FAS population)

Glucose metabolism markers (A1c, HOMA-IR, glucose, insulin) by visit with hepatic

fat fraction sub-groups as stratification factor (ITT populations)

Glucose metabolism markers (A1c, HOMA-IR, glucose, insulin) by visit with hepatic fat fraction sub-groups as stratification factor (PP population)

Glucose metabolism markers (A1c, HOMA-IR, glucose, insulin) by visit with HbA1c sub-groups as stratification factor (FAS population)

Glucose metabolism markers (A1c, HOMA-IR, glucose, insulin) by visit with HbA1c sub-groups as stratification factor (ITT populations)

Glucose metabolism markers (A1c, HOMA-IR, glucose, insulin) by visit with HbA1c sub-groups as stratification factor (PP population)

Glucose metabolism markers (A1c, HOMA-IR, glucose, insulin) by visit with Fibrosis sub-groups as stratification factor (FAS population)

Glucose metabolism markers (A1c, HOMA-IR, glucose, insulin) by visit with Fibrosis sub-groups as stratification factor (ITT populations)

Glucose metabolism markers (A1c, HOMA-IR, glucose, insulin) by visit with Fibrosis sub-groups as stratification factor (PP population)

Glucose metabolism markers (A1c, HOMA-IR, glucose, insulin) by visit with Ballooning sub-groups as stratification factor (FAS population)

Glucose metabolism markers (A1c, HOMA-IR, glucose, insulin) by visit with Ballooning sub-groups as stratification factor (ITT populations)

Glucose metabolism markers (A1c, HOMA-IR, glucose, insulin) by visit with Ballooning sub-groups as stratification factor (PP population)

Glucose metabolism markers (A1c, HOMA-IR, glucose, insulin) by visit with Inflammation sub-groups as stratification factor (FAS population)

Glucose metabolism markers (A1c, HOMA-IR, glucose, insulin) by visit with Inflammation sub-groups as stratification factor (ITT populations)

Glucose metabolism markers (A1c, HOMA-IR, glucose, insulin) by visit with Inflammation sub-groups as stratification factor (PP population)

Glucose metabolism markers (A1c, HOMA-IR, glucose, insulin) by visit with ALT sub-groups as stratification factor (FAS population)

Glucose metabolism markers (A1c, HOMA-IR, glucose, insulin) by visit with ALT sub-groups as stratification factor (ITT populations)

Glucose metabolism markers (A1c, HOMA-IR, glucose, insulin) by visit with ALT sub-groups as stratification factor (PP population)

Body mass index, waist circumference and waist:hip ratio by visit (FAS population)

Body mass index, waist circumference and waist:hip ratio by visit (ITT population)

Body mass index, waist circumference and waist:hip ratio by visit (PP population)

Body mass index, waist circumference and waist:hip ratio by visit with hepatic fat fraction sub-groups as stratification factor (FAS population)

Body mass index, waist circumference and waist:hip ratio by visit with hepatic fat fraction sub-groups as stratification factor (ITT population)

Body mass index, waist circumference and waist:hip ratio by visit with hepatic fat fraction sub-groups as stratification factor (PP population)

Body mass index, waist circumference and waist:hip ratio by visit with HbA1c sub-groups as stratification factor (FAS population)

Body mass index, waist circumference and waist:hip ratio by visit with HbA1c sub-

groups as stratification factor (ITT population)

Body mass index, waist circumference and waist:hip ratio by visit with HbA1c sub-groups as stratification factor (PP population)

Body mass index, waist circumference and waist:hip ratio by visit with Fibrosis sub-groups as stratification factor (FAS population)

Body mass index, waist circumference and waist:hip ratio by visit with Fibrosis sub-groups as stratification factor (ITT population)

Body mass index, waist circumference and waist:hip ratio by visit with Fibrosis sub-groups as stratification factor (PP population)

Body mass index, waist circumference and waist:hip ratio by visit with Ballooning sub-groups as stratification factor (FAS population)

Body mass index, waist circumference and waist:hip ratio by visit with Ballooning sub-groups as stratification factor (ITT population)

Body mass index, waist circumference and waist:hip ratio by visit with Ballooning sub-groups as stratification factor (PP population)

Body mass index, waist circumference and waist:hip ratio by visit with Inflammation sub-groups as stratification factor (FAS population)

Body mass index, waist circumference and waist:hip ratio by visit with Inflammation sub-groups as stratification factor (ITT population)

Body mass index, waist circumference and waist:hip ratio by visit with Inflammation sub-groups as stratification factor (PP population)

Body mass index, waist circumference and waist:hip ratio by visit with ALT sub-groups as stratification factor (FAS population)

Body mass index, waist circumference and waist:hip ratio by visit with ALT sub-groups as stratification factor (ITT population)

Body mass index, waist circumference and waist:hip ratio by visit with ALT sub-groups as stratification factor (PP population)

Serum lipid profile by visit (FAS population)

Serum lipid profile by visit (ITT population)

Serum lipid profile by visit (PP population)

Serum lipid profile by visit with hepatic fat fraction sub-groups as stratification factor (FAS population)

Serum lipid profile by visit with hepatic fat fraction sub-groups as stratification factor (ITT population)

Serum lipid profile by visit with hepatic fat fraction sub-groups as stratification factor (PP population)

Serum lipid profile by visit with HbA1c sub-groups as stratification factor (FAS population)

Serum lipid profile by visit with HbA1c sub-groups as stratification factor (ITT population)

Serum lipid profile by visit with HbA1c sub-groups as stratification factor (PP population)

Serum lipid profile by visit with Fibrosis sub-groups as stratification factor (FAS population)

Serum lipid profile by visit with Fibrosis sub-groups as stratification factor (ITT

population)

Serum lipid profile by visit with Fibrosis sub-groups as stratification factor (PP population)

Serum lipid profile by visit with Ballooning sub-groups as stratification factor (FAS population)

Serum lipid profile by visit with Ballooning sub-groups as stratification factor (ITT population)

Serum lipid profile by visit with Ballooning sub-groups as stratification factor (PP population)

Serum lipid profile by visit with Inflammation sub-groups as stratification factor (FAS population)

Serum lipid profile by visit with Inflammation sub-groups as stratification factor (ITT population)

Serum lipid profile by visit with Inflammation sub-groups as stratification factor (PP population)

Serum lipid profile by visit with ALT sub-groups as stratification factor (FAS population)

Serum lipid profile by visit with ALT sub-groups as stratification factor (ITT population)

Serum lipid profile by visit with ALT sub-groups as stratification factor (PP population)

Liver function profile (ALT, AST, GGT, Bilirubin, albumin) by visit (FAS population)

Liver function profile (ALT, AST, GGT, Bilirubin, albumin) by visit (ITT population)

Liver function profile (ALT, AST, GGT, Bilirubin, albumin) by visit (PP population)

Liver function profile (ALT, AST, GGT, Bilirubin, albumin) by visit with hepatic fat fraction sub-groups as stratification factor (FAS population)

Liver function profile (ALT, AST, GGT, Bilirubin, albumin) by visit with hepatic fat fraction sub-groups as stratification factor (ITT population)

Liver function profile (ALT, AST, GGT, Bilirubin, albumin) by visit with hepatic fat fraction sub-groups as stratification factor (PP population)

Liver function profile (ALT, AST, GGT, Bilirubin, albumin) by visit with HbA1c sub-groups as stratification factor (FAS population)

Liver function profile (ALT, AST, GGT, Bilirubin, albumin) by visit with HbA1c sub-groups as stratification factor (ITT population)

Liver function profile (ALT, AST, GGT, Bilirubin, albumin) by visit with HbA1c sub-groups as stratification factor (PP population)

Liver function profile (ALT, AST, GGT, Bilirubin, albumin) by visit with Fibrosis sub-groups as stratification factor (FAS population)

Liver function profile (ALT, AST, GGT, Bilirubin, albumin) by visit with Fibrosis sub-groups as stratification factor (ITT population)

Liver function profile (ALT, AST, GGT, Bilirubin, albumin) by visit with Fibrosis sub-groups as stratification factor (PP population)

Liver function profile (ALT, AST, GGT, Bilirubin, albumin) by visit with Ballooning sub-groups as stratification factor (FAS population)

Liver function profile (ALT, AST, GGT, Bilirubin, albumin) by visit with Ballooning

sub-groups as stratification factor (ITT population)

Liver function profile (ALT, AST, GGT, Bilirubin, albumin) by visit with Ballooning sub-groups as stratification factor (PP population)

Liver function profile (ALT, AST, GGT, Bilirubin, albumin) by visit with Inflammation sub-groups as stratification factor (FAS population)

Liver function profile (ALT, AST, GGT, Bilirubin, albumin) by visit with Inflammation sub-groups as stratification factor (ITT population)

Liver function profile (ALT, AST, GGT, Bilirubin, albumin) by visit with Inflammation sub-groups as stratification factor (PP population)

Liver function profile (ALT, AST, GGT, Bilirubin, albumin) by visit with ALT sub-groups as stratification factor (FAS population)

Liver function profile (ALT, AST, GGT, Bilirubin, albumin) by visit with ALT sub-groups as stratification factor (ITT population)

Liver function profile (ALT, AST, GGT, Bilirubin, albumin) by visit with ALT sub-groups as stratification factor (PP population)

Biomarker and cytokine profile by visit (FAS population)

Biomarker and cytokine profile by visit (ITT population)

Biomarker and cytokine profile by visit (PP population)

Biomarker and cytokine profile by visit with hepatic fat fraction sub-groups as stratification factor (FAS population)

Biomarker and cytokine profile by visit with hepatic fat fraction sub-groups as stratification factor (ITT population)

Biomarker and cytokine profile by visit with hepatic fat fraction sub-groups as stratification factor (PP population)

Biomarker and cytokine profile by visit with HbA1c sub-groups as stratification factor (FAS population)

Biomarker and cytokine profile by visit with HbA1c sub-groups as stratification factor (ITT population)

Biomarker and cytokine profile by visit with HbA1c sub-groups as stratification factor (PP population)

Biomarker and cytokine profile by visit with Fibrosis sub-groups as stratification factor (FAS population)

Biomarker and cytokine profile by visit with Fibrosis sub-groups as stratification factor (ITT population)

Biomarker and cytokine profile by visit with Fibrosis sub-groups as stratification factor (PP population)

Biomarker and cytokine profile by visit with Ballooning sub-groups as stratification factor (FAS population)

Biomarker and cytokine profile by visit with Ballooning sub-groups as stratification factor (ITT population)

Biomarker and cytokine profile by visit with Ballooning sub-groups as stratification factor (PP population)

Biomarker and cytokine profile by visit with Inflammation sub-groups as stratification factor (FAS population)

Biomarker and cytokine profile by visit with Inflammation sub-groups as

stratification factor (ITT population)

Biomarker and cytokine profile by visit with Inflammation sub-groups as stratification factor (PP population)

Biomarker and cytokine profile by visit with ALT sub-groups as stratification factor (FAS population)

Biomarker and cytokine profile by visit with ALT sub-groups as stratification factor (ITT population)

Biomarker and cytokine profile by visit with ALT sub-groups as stratification factor (PP population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of hepatic fat from baseline (FAS population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of hepatic fat from baseline (ITT population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of hepatic fat from baseline (PP population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of hepatic fat from baseline with hepatic fat fraction sub-groups as stratification factor (FAS population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of hepatic fat from baseline with hepatic fat fraction sub-groups as stratification factor (ITT population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of hepatic fat from baseline with hepatic fat fraction sub-groups as stratification factor (PP population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of hepatic fat from baseline with HbA1c sub-groups as stratification factor (FAS population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of hepatic fat from baseline with HbA1c sub-groups as stratification factor (ITT population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of hepatic fat from baseline with HbA1c sub-groups as stratification factor (PP population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of hepatic fat from baseline with Fibrosis sub-groups as stratification factor (FAS population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of hepatic fat from baseline with Fibrosis sub-groups as stratification factor (ITT population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of hepatic fat from baseline with Fibrosis sub-groups as stratification factor (PP population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of hepatic fat from baseline with Ballooning sub-groups as stratification factor (FAS population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of hepatic fat from baseline with Ballooning sub-groups as stratification factor (ITT population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of hepatic fat from baseline with Ballooning sub-groups as stratification factor (PP population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of hepatic fat from baseline with Inflammation sub-groups as stratification factor (FAS population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of hepatic fat from baseline with Inflammation sub-groups as stratification factor (ITT population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of hepatic fat from

baseline with Inflammation sub-groups as stratification factor (PP population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of hepatic fat from baseline with ALT sub-groups as stratification factor (FAS population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of hepatic fat from baseline with ALT sub-groups as stratification factor (ITT population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of hepatic fat from baseline with ALT sub-groups as stratification factor (PP population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of ALT, AST and HbA1c from baseline (FAS population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of ALT, AST and HbA1c from baseline (ITT population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of ALT, AST and HbA1c from baseline (PP population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of ALT, AST and HbA1c from baseline with hepatic fat fraction sub-groups as stratification factor (FAS population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of ALT, AST and HbA1c from baseline with hepatic fat fraction sub-groups as stratification factor (ITT population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of ALT, AST and HbA1c from baseline with hepatic fat fraction sub-groups as stratification factor (PP population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of ALT, AST and HbA1c from baseline with HbA1c sub-groups as stratification factor (FAS population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of ALT, AST and HbA1c from baseline with HbA1c sub-groups as stratification factor (ITT population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of ALT, AST and HbA1c from baseline with HbA1c sub-groups as stratification factor (PP population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of ALT, AST and HbA1c from baseline with Fibrosis sub-groups as stratification factor (FAS population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of ALT, AST and HbA1c from baseline with Fibrosis sub-groups as stratification factor (ITT population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of ALT, AST and HbA1c from baseline with Fibrosis sub-groups as stratification factor (PP population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of ALT, AST and HbA1c from baseline with Ballooning sub-groups as stratification factor (FAS population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of ALT, AST and HbA1c from baseline with Ballooning sub-groups as stratification factor (ITT population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of ALT, AST and HbA1c from baseline with Ballooning sub-groups as stratification factor (PP population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of ALT, AST and HbA1c from baseline with Inflammation sub-groups as stratification factor (FAS population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of ALT, AST and HbA1c from baseline with Inflammation sub-groups as stratification factor (ITT population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of ALT, AST and HbA1c from baseline with Inflammation sub-groups as stratification factor (PP population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of ALT, AST and HbA1c from baseline with ALT sub-groups as stratification factor (FAS population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of ALT, AST and HbA1c from baseline with ALT sub-groups as stratification factor (ITT population)

Proportion of subjects with 5%, 10%, 20% and 30% reduction of ALT, AST and HbA1c from baseline with ALT sub-groups as stratification factor (PP population)

Correlations between change in hepatic fat fraction and ALT, AST, C-reactive protein, A1c and LPS (FAS population)

Correlations between change in hepatic fat fraction and ALT, AST, C-reactive protein, A1c and LPS (ITT population)

Correlations between change in hepatic fat fraction and ALT, AST, C-reactive protein, A1c and LPS (PP population)

Correlations between change in hepatic fat fraction and ALT, AST, C-reactive protein, A1c and LPS with hepatic fat fraction sub-groups as stratification factor (FAS population)

Correlations between change in hepatic fat fraction and ALT, AST, C-reactive protein, A1c and LPS with hepatic fat fraction sub-groups as stratification factor (ITT population)

Correlations between change in hepatic fat fraction and ALT, AST, C-reactive protein, A1c and LPS with hepatic fat fraction sub-groups as stratification factor (PP population)

Correlations between change in hepatic fat fraction and ALT, AST, C-reactive protein, A1c and LPS with HbA1c sub-groups as stratification factor (FAS population)

Correlations between change in hepatic fat fraction and ALT, AST, C-reactive protein, A1c and LPS with HbA1c sub-groups as stratification factor (ITT population)

Correlations between change in hepatic fat fraction and ALT, AST, C-reactive protein, A1c and LPS with HbA1c sub-groups as stratification factor (PP population)

Correlations between change in hepatic fat fraction and ALT, AST, C-reactive protein, A1c and LPS with Fibrosis sub-groups as stratification factor (FAS population)

Correlations between change in hepatic fat fraction and ALT, AST, C-reactive protein, A1c and LPS with Fibrosis sub-groups as stratification factor (ITT population)

Correlations between change in hepatic fat fraction and ALT, AST, C-reactive protein, A1c and LPS with Fibrosis sub-groups as stratification factor (PP population)

Correlations between change in hepatic fat fraction and ALT, AST, C-reactive protein, A1c and LPS with Ballooning sub-groups as stratification factor (FAS

population)

Correlations between change in hepatic fat fraction and ALT, AST, C-reactive protein, A1c and LPS with Ballooning sub-groups as stratification factor (ITT population)

Correlations between change in hepatic fat fraction and ALT, AST, C-reactive protein, A1c and LPS with Ballooning sub-groups as stratification factor (PP population)

Correlations between change in hepatic fat fraction and ALT, AST, C-reactive protein, A1c and LPS with Inflammation sub-groups as stratification factor (FAS population)

Correlations between change in hepatic fat fraction and ALT, AST, C-reactive protein, A1c and LPS with Inflammation sub-groups as stratification factor (ITT population)

Correlations between change in hepatic fat fraction and ALT, AST, C-reactive protein, A1c and LPS with Inflammation sub-groups as stratification factor (PP population)

Correlations between change in hepatic fat fraction and ALT, AST, C-reactive protein, A1c and LPS with ALT sub-groups as stratification factor (FAS population)

Correlations between change in hepatic fat fraction and ALT, AST, C-reactive protein, A1c and LPS with ALT sub-groups as stratification factor (ITT population)

Correlations between change in hepatic fat fraction and ALT, AST, C-reactive protein, A1c and LPS with ALT sub-groups as stratification factor (PP population)

PBMCs with change from Baseline by visit (FAS population)

PBMCs with change from Baseline by visit (ITT population)

PBMCs with change from Baseline by visit (PP population)

PBMCs with change from Baseline by visit with hepatic fat fraction sub-groups as stratification factor (FAS population)

PBMCs with change from Baseline by visit with hepatic fat fraction sub-groups as stratification factor (ITT population)

PBMCs with change from Baseline by visit with hepatic fat fraction sub-groups as stratification factor (PP population)

PBMCs with change from Baseline by visit with HbA1c sub-groups as stratification factor (FAS population)

PBMCs with change from Baseline by visit with HbA1c sub-groups as stratification factor (ITT population)

PBMCs with change from Baseline by visit with HbA1c sub-groups as stratification factor (PP population)

PBMCs with change from Baseline by visit with Fibrosis sub-groups as stratification factor (FAS population)

PBMCs with change from Baseline by visit with Fibrosis sub-groups as stratification factor (ITT population)

PBMCs with change from Baseline by visit with Fibrosis sub-groups as stratification factor (PP population)

PBMCs with change from Baseline by visit with Ballooning sub-groups as stratification factor (FAS population)

PBMCs with change from Baseline by visit with Ballooning sub-groups as

stratification factor (ITT population)

PBMCs with change from Baseline by visit with Ballooning sub-groups as stratification factor (PP population)

PBMCs with change from Baseline by visit with Inflammation sub-groups as stratification factor (FAS population)

PBMCs with change from Baseline by visit with Inflammation sub-groups as stratification factor (ITT population)

PBMCs with change from Baseline by visit with Inflammation sub-groups as stratification factor (PP population)

PBMCs with change from Baseline by visit with ALT sub-groups as stratification factor (FAS population)

PBMCs with change from Baseline by visit with ALT sub-groups as stratification factor (ITT population)

PBMCs with change from Baseline by visit with ALT sub-groups as stratification factor (PP population)

C-reactive protein with change from Baseline by visit (FAS population)

C-reactive protein with change from Baseline by visit (ITT population)

C-reactive protein with change from Baseline by visit (PP population)

C-reactive protein with change from Baseline by visit with hepatic fat fraction sub-groups as stratification factor (FAS population)

C-reactive protein with change from Baseline by visit with hepatic fat fraction sub-groups as stratification factor (ITT population)

C-reactive protein with change from Baseline by visit with hepatic fat fraction sub-groups as stratification factor (PP population)

C-reactive protein with change from Baseline by visit with HbA1c sub-groups as stratification factor (FAS population)

C-reactive protein with change from Baseline by visit with HbA1c sub-groups as stratification factor (ITT population)

C-reactive protein with change from Baseline by visit with HbA1c sub-groups as stratification factor (PP population)

C-reactive protein with change from Baseline by visit with Fibrosis sub-groups as stratification factor (FAS population)

C-reactive protein with change from Baseline by visit with Fibrosis sub-groups as stratification factor (ITT population)

C-reactive protein with change from Baseline by visit with Fibrosis sub-groups as stratification factor (PP population)

C-reactive protein with change from Baseline by visit with Ballooning sub-groups as stratification factor (FAS population)

C-reactive protein with change from Baseline by visit with Ballooning sub-groups as stratification factor (ITT population)

C-reactive protein with change from Baseline by visit with Ballooning sub-groups as stratification factor (PP population)

C-reactive protein with change from Baseline by visit with Inflammation sub-groups as stratification factor (FAS population)

C-reactive protein with change from Baseline by visit with Inflammation sub-groups

as stratification factor (ITT population)

C-reactive protein with change from Baseline by visit with Inflammation sub-groups as stratification factor (PP population)

C-reactive protein with change from Baseline by visit with ALT sub-groups as stratification factor (FAS population)

C-reactive protein with change from Baseline by visit with ALT sub-groups as stratification factor (ITT population)

C-reactive protein with change from Baseline by visit with ALT sub-groups as stratification factor (PP population)

Fibrosis-4 Score with change from Baseline by visit (FAS population)

Fibrosis-4 Score with change from Baseline by visit (ITT population)

Fibrosis-4 Score with change from Baseline by visit (PP population)

Fibrosis-4 Score with change from Baseline by visit with hepatic fat fraction sub-groups as stratification factor (FAS population)

Fibrosis-4 Score with change from Baseline by visit with hepatic fat fraction sub-groups as stratification factor (ITT population)

Fibrosis-4 Score with change from Baseline by visit with hepatic fat fraction sub-groups as stratification factor (PP population)

Fibrosis-4 Score with change from Baseline by visit with HbA1c sub-groups as stratification factor (FAS population)

Fibrosis-4 Score with change from Baseline by visit with HbA1c sub-groups as stratification factor (ITT population)

Fibrosis-4 Score with change from Baseline by visit with HbA1c sub-groups as stratification factor (PP population)

Fibrosis-4 Score with change from Baseline by visit with Fibrosis sub-groups as stratification factor (FAS population)

Fibrosis-4 Score with change from Baseline by visit with Fibrosis sub-groups as stratification factor (ITT population)

Fibrosis-4 Score with change from Baseline by visit with Fibrosis sub-groups as stratification factor (PP population)

Fibrosis-4 Score with change from Baseline by visit with Ballooning sub-groups as stratification factor (FAS population)

Fibrosis-4 Score with change from Baseline by visit with Ballooning sub-groups as stratification factor (ITT population)

Fibrosis-4 Score with change from Baseline by visit with Ballooning sub-groups as stratification factor (PP population)

Fibrosis-4 Score with change from Baseline by visit with Inflammation sub-groups as stratification factor (FAS population)

Fibrosis-4 Score with change from Baseline by visit with Inflammation sub-groups as stratification factor (ITT population)

Fibrosis-4 Score with change from Baseline by visit with Inflammation sub-groups as stratification factor (PP population)

Fibrosis-4 Score with change from Baseline by visit with ALT sub-groups as stratification factor (FAS population)

Fibrosis-4 Score with change from Baseline by visit with ALT sub-groups as

stratification factor (ITT population)

Fibrosis-4 Score with change from Baseline by visit with ALT sub-groups as stratification factor (PP population)

Pharmacokinetic measures of IMM-124E bovine antibodies by visit (FAS population)

Pharmacokinetic measures of IMM-124E bovine antibodies by visit (ITT population)

Pharmacokinetic measures of IMM-124E bovine antibodies by visit (PP population)

Serum concentrations of IMM-214E bovine antibodies by visit and time point (FAS population)

Serum concentrations of IMM-214E bovine antibodies by visit and time point (ITT population)

Serum concentrations of IMM-214E bovine antibodies by visit and time point (PP populations)

MELD score with change by visit (FAS population)

MELD score with change by visit (ITT population)

MELD score with change by visit (PP population)

MELD score with change by visit with hepatic fat fraction sub-groups as stratification factor (FAS population)

MELD score with change by visit with hepatic fat fraction sub-groups as stratification factor (ITT population)

MELD score with change by visit with hepatic fat fraction sub-groups as stratification factor (PP population)

MELD score with change by visit with HbA1c sub-groups as stratification factor (FAS population)

MELD score with change by visit with HbA1c sub-groups as stratification factor (ITT population)

MELD score with change by visit with HbA1c sub-groups as stratification factor (PP population)

MELD score with change by visit with Fibrosis sub-groups as stratification factor (FAS population)

MELD score with change by visit with Fibrosis sub-groups as stratification factor (ITT population)

MELD score with change by visit with Fibrosis sub-groups as stratification factor (PP population)

MELD score with change by visit with Ballooning sub-groups as stratification factor (FAS population)

MELD score with change by visit with Ballooning sub-groups as stratification factor (ITT population)

MELD score with change by visit with Ballooning sub-groups as stratification factor (PP population)

MELD score with change by visit with Inflammation sub-groups as stratification factor (FAS population)

MELD score with change by visit with Inflammation sub-groups as stratification factor (ITT population)

	MELD score with change by visit with Inflammation sub-groups as stratification factor (PP population)
	MELD score with change by visit with ALT sub-groups as stratification factor (FAS population)
	MELD score with change by visit with ALT sub-groups as stratification factor (ITT population)
	MELD score with change by visit with ALT sub-groups as stratification factor (PP population)
Section 12.1	Exposure
Section 12.2	Adverse events summary
	Adverse events occurring prior to study treatment (if any) (Safety and ET populations)
	Most common (≥10%) treatment emergent adverse events by Preferred Term (Safety population)
	Treatment emergent adverse events leading to withdrawal (Safety and ET populations)
	Exploratory table including baseline and final values (ET population)
Section 14.1	Medical history (Safety and ET populations)
	Physical Examination(Safety population)
	12-lead ECG (Safety population)
	Prior medications (Safety and ET populations)
	Concomitant medications (Safety and ET populations)
	New medications (Safety and ET populations)
	Urinalysis at Screening (Safety population)
Section 14.3	Treatment emergent adverse events (Safety and ET populations)
	Treatment emergent adverse events that were possibly, probably or definitely related to the study medication (Safety and ET populations)
	Serious adverse events (Safety and ET populations)
	Severe adverse events (Safety and ET populations)
	Treatment emergent adverse events by maximum severity and relationship to study treatment, with subject identification (Safety population)
Section 14.4	Serum Biochemistry by visit (Safety population)
	Shift table of serum biochemistry by visit (Safety population)
	Haematology by visit (Safety population)
	Shift table of haematology by visit (Safety population)
	Vital signs by visit (Safety population)
	Physical examination results by visit

Figure Section	Figure Title (Population)
Section 11.4	Difference in hepatic fat between Placebo and each dose level of IMM-124E (ITT, PP, FAS populations)
	Difference in hepatic fat between Placebo and each dose level of IMM-124E by hepatic fat category and HbA1c (ITT, PP, FAS populations) (lattice graph)
	Difference in hepatic fat between Placebo and each dose level of IMM-124E (ITT, PP, FAS populations with MI imputation where appropriate)
	Difference in hepatic fat between Placebo and each dose level of IMM-124E by hepatic fat category and HbA1c (ITT, PP, FAS populations with MI imputation where appropriate) (lattice graph)
	Proportion of subjects with normal ALT by visit (ITT, PP, FAS populations)
	MELD score by visit (ITT, PP, FAS populations)
	Proportion of subjects with 5% reduction of hepatic fat from baseline (ITT, PP, FAS populations)
	Proportion of subjects with 10% reduction of hepatic fat from baseline (ITT, PP, FAS populations)
	Body mass index, waist circumference and waist:hip ratio by visit (ITT, PP, FAS populations)
	HbA1c by visit (ITT, PP, FAS populations)
	HOMA-IR by visit (ITT, PP, FAS populations)
	AUDIT results by visit (ITT, PP, FAS populations)
Section 12.2	Odds ratios of most common Preferred Terms (Safety population)

Sample Tables

Primary analysis

										Group comparisons					
Treatment	**Visit / Value**	**n**	**Mean**	**SD**	**Median**	**Quartiles 1 & 3**	**Min**	**Max**	**Prob = 0**	**Normality Prob**	**Change**	**Ranks Prob**	**Ranks**	**Permut ations**	**Disp-arity**
Treatment 1	Screening														
	Baseline														
	Timepoint 1														
	Change to Timepoint 1														
	Adj change to Timepoint 1														
	Difference from Treatment 2														
	Difference from Treatment 3														
	Change to Timepoint 2…														

Primary analysis with Subgrouping

											Group comparisons					
Subgroup (e.g. HFF, A1c, ALT, Fibrosis, Inflammation , ballooning)	**Treatment**	**Visit / Value**	**n**	**Mean**	**SD**	**Median**	**Quartiles 1 & 3**	**Min**	**Max**	**Prob = 0**	**Normality Prob**	**Change**	**Ranks Prob**	**Ranks**	**Permut ations**	**Disp-arity**
Group 1	Treatment 1	Screening														
		Baseline														
		Timepoint 1														
		Change to Timepoint 1														
		Adj change to Timepoint 1														
		Difference from Treatment 2														
		Difference from Treatment 3														
		Change to Timepoint 2…														
	Treatment 2	Screening														
		Baseline														
		Timepoint 1														
		Change to Timepoint 1														

											Group comparisons					
Subgroup (e.g. HFF, A1c, ALT, Fibrosis, Inflammation , ballooning)	**Treatment**	**Visit / Value**	**n**	**Mean**	**SD**	**Median**	**Quartiles 1 & 3**	**Min**	**Max**	**Prob = 0**	**Normality Prob**	**Change**	**Ranks Prob**	**Ranks**	**Permut ations**	**Disp-arity**
		Adj change to Timepoint 1														
		Difference from Treatment 2														
		Difference from Treatment 3														
		Change to Timepoint 2…														

13. APPENDIX 1 – EXTENSION OF WILCOXON RANK-SUM TEST FOR CLUSTERED DATA

Adapted from Lehmann, 2006:

To compare each one of the treatment arms to the placebo arm separately, perform the following steps:

1. Each FF category at baseline will be defined as a separate cluster.
2. Within each cluster, rank all values (treatment and placebo together)
3. Calculate w_i which is the sum of ranks of the treatment group in each cluster separately.
4. Calculate $W = \sum_{i=1}^{M} w_i$ while M is the total number of clusters.
5. The best way to test *W* is by using a **permutation test**. This may be computationally too complex to apply. If so, there is a normal distribution approximation we can use but it is less accurate, especially in our small sample so, if possible, we advise to try and use the permutation test.

   The permutation should be performed so we protect the data of each cluster separately and also protect the cluster design of the sample.

   More specifically, Let us define:
   n_i- the number of observations in cluster *i*.
   n_{i0}- the number of observations in cluster *i*, in the placebo arm.
   n_{i1}- the number of observations in cluster *i*, in the treatment arm.
   Each permutation will be calculated by randomly sampling n_{i1} values within each cluster from the n_i values available and calculating the rank sum of those values. Going over all possible permutation of the data under this design.