STATISTICAL ANALYSIS PLAN

REMIT-Sita

An open-label, randomized, parallel design trial to compare the efficacy of a sitagliptin-based metabolic intervention versus standard diabetes therapy in inducing remission of type 2 diabetes

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LIST OF ABBREVIATIONS

The following abbreviations and special terms are used

Abbreviation or special term	Explanation
ALT	alanine transferase
BhCG	beta human chorionic gonadotropin
bid	twice daily
BMI	body mass index
BP	Blood Pressure
CDA	Canadian Diabetes Association
CI	Confidence Interval
Cr	creatinine
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
FPG	fasting plasma glucose
MDRD	The Modification of Diet in Renal Disease equation to estimate GFR
OD	once daily
OGTT	Oral Glucose Tolerance Test
PA	physical activity
pc	postcibum (postprandial)
PHRI	Population Health Research Institute
po	taken orally
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
sc	taken subcutaneously
SD	Standard Deviation
SGLT2	sodium glucose co-transporter 2
SMBG	self-monitoring of capillary blood glucose
T2DM	type 2 diabetes mellitus
WHR	Waist Hip Ratio

1. INTRODUCTION

The statistical analysis plan (SAP) specifies the details of the statistical analysis of the REMIT-Sita trial described in the Clinical Study Protocol (version 2.0, dated 2015-12-16). The SAP is a working document that will be amended as new information becomes available. Appendices may be updated as required during the course of the study. The final version of the SAP will be signed off prior to database lock.

REMIT-Sita is a multicentre, open-label, randomized controlled trial in 102 patients with recently-diagnosed T2DM. Participants will be randomized to 2 treatment groups: (a) a 12-week course of treatment with sitagliptin, metformin, insulin glargine and lifestyle therapy, and (b) standard diabetes therapy, and followed for a total of 64 weeks (1 year and 3 months). In all participants with HbA1C<7.3%, glucose-lowering medications will be discontinued at 12 weeks, and participants will be encouraged to continue with lifestyle modifications and regular glucose monitoring. Participants who meet criteria for hyperglycemia relapse will receive standard glycemic management as informed by the 2013 Canadian Diabetes Association clinical practice guidelines.

The primary outcome in this trial will be hyperglycemia relapse at or after the 12-week visit. The primary safety outcome will be the rate of severe hypoglycemic episodes during 64 weeks of follow-up. Key secondary outcomes will be diabetes remission at 24, 36, 48 and 64 weeks and drug-free normal glucose tolerance at 24 weeks.

Glycemic outcome definitions for this trial are summarized in the following table:

Drug-free normal glucose tolerance	**Diabetes remission**	**Hyperglycemia relapse**
FPG* <6.1 mmol/L AND 2-hour plasma glucose <7.8 mmol/L on OGTT†	HbA1C <6.5% AND no diabetes drugs for ≥12 weeks AND no relapse	HbA1C ≥6.5% OR FPG* ≥7.0 mmol/L OR 2-hour postprandial plasma glucose ≥11.1 mmol/L on OGTT† OR Use of diabetes drugs OR Capillary glucose ≥10 mmol/L on ≥50% SMBGs‡ over 1 week

*FPG – fasting plasma glucose
†OGTT – 75 g oral glucose tolerance test at 24 weeks
‡SMBG – self-monitoring of blood glucose

2. STUDY OBJECTIVES

Primary objective

To determine whether the 12-week metabolic intervention that includes sitagliptin is more efficacious in achieving drug-free remission of type 2 diabetes than standard diabetes therapy over 1 year following the 12-week induction period.

Secondary objective

To determine whether the 12-week metabolic intervention that includes sitagliptin is more efficacious than standard diabetes therapy in achieving diabetes remission when evaluated at 24, 36, 48 and 64 weeks after randomization.

Safety objective

To determine the rates of severe hypoglycemic episodes in the treatment groups during 64 weeks of follow-up.

3. POPULATIONS TO BE ANALYZED

All randomized participants will be included in the treatment groups to which they were randomized, regardless of treatments received or duration of trial participation (intention-to-treat analysis).

4. BASELINE CHARACTERISTICS

Standard methods will be used to provide tabular and graphical summaries as appropriate for continuous and categorical variables. Summaries of continuous variables will include the number of subjects (N), mean, standard deviation, median, minimum and maximum. Frequency distributions (N and %) will be given for categorical data.

Summary Tables of Baseline characteristics are in Appendix A.

5. ADHERENCE

Visit adherence

Adherence to the visit schedule will be summarized by visit (after randomization) and treatment group as follows:

- total number of participants enrolled in trial (N)
- frequency and percentage of participants who have completed due visit (or provided information by phone or other means)
- frequency and percentage of participants who have refused visit
- frequency and percentage of participants who were unable to be contacted for visit
- frequency and percentage of participants who died prior to due visit

Note: participants who died prior to visit X will be excluded for the count of "due" visit at visit X+1 and onwards.

Tables are in Appendix A

Medication adherence

Adherence with the study medications in the intervention group will be summarized by visit (randomization and follow-up), up until the end of the intervention period, in order to assess tolerability, as follows:

- total number of participants enrolled (N)
- percentage of participants who have completed visit
- percentage of participants taking each study medication
- percentage of participants taking all study medications

Study medication can be stopped without the need for unblinding as it is an open label trial.

6. STUDY FOLLOW-UP TIME

Clinic visits for all participants will occur at enrolment (screening and randomization) and weeks 6, 12, 24, 36, and 48. Telephone visits will occur at weeks 12.5, 20, 28, 32, 40, 44, 52, 56, and 60. A final visit will take place at week 64 of follow-up for each participant (1 year and 3 months after randomization). All efforts will be made to collect complete data for all participants in this study, regardless of their compliance with study medications.

In general, missing values within follow up will be treated as 'missing' and no attempt will be made to impute missing post-randomization values and only observed values will be used for analysis. Diabetes remission and regression status will be imputed as indicated in Section 3 of Appendix A and in Appendix B.

Lost to follow-up

All efforts will be made to collect information about the clinical outcomes for those participants who were lost to follow-up.

Missing date information

When an event date is not known, the site investigator will be asked to provide a best estimate as to when the event occurred. Even though the exact date of an event is unknown, the investigator often does know some information that would indicate the approximate date, such as the first week of a month, in the fall of a year, or the middle of a particular year or at least the date when the patient was last seen or contacted. This information can be meaningfully incorporated into the estimated date recorded, as this is likely to be will be closer to the true date than any produced by an uninformed computer program. This estimated date should be the middle date within the period that the event is known to have occurred. If the event is known to have occurred in the first week of a month, then the date in the middle of that week should be recorded as the estimate. If it

occurred in the fall of a year, then the middle date in the fall is the appropriate estimate. If no information is known then the date in the middle of the plausible time period should be given, based on the last contact with the patient prior to the event and the date of contact when information about the event was known. This method for date estimation has been used in many studies and is recommended by Dubois and Hebert (Dubois & Hebert 2001).

Baseline, Time Windows and Calculated Visits

The randomization visit (Day 0) is the reference for all time-related analyses unless otherwise indicated.

It is expected that the study period will include up to 64 weeks of follow-up visits based on the REMIT-Sita protocol.

7. EFFICACY ANALYSES

Primary Outcome

The primary outcome in this trial will be hyperglycemia relapse at or after the 12-week visit. Time to Relapse analysis will be conducted using a Cox Proportional Hazards Model. Kaplan-Meier curves will be plotted and compared using a log-rank test. Hazard ratio with 95% CI will be obtained form the Cox Proportional Hazards Model. If Proportional Hazard assumption is not held, K-M curves will be compared using Wilcoxon test.

Primary Safety Outcome

Proportion of participants with severe hypoglycemia during 64 weeks of follow-up in each treatment group.

Key Secondary Outcomes at Pre-specified Time Points

Proportion of participants with diabetes remission will be calculated at 24, 36, 48 and 64 weeks after randomization.

Drug-free normal glucose tolerance will be calculated based on the oral glucose tolerance test at 24 weeks. This outcome can occur regardless of relapse as participants taking glucose-lowering medications were asked to hold them prior to the test.

The primary and secondary analyses will be based on the intention to treat principle, i.e. with participants analyzed in the treatment group to which they were randomized. Primary safety analysis and all secondary analyses will be exploratory. Unadjusted differences in risk between the treatment groups will be assessed by a generalized linear model and presented as relative risk with 95% CI. P value will be presented from Chi-Square test. Tests of significance will be 2-sided with Type I error of 5% and no adjustment for multiple testing.

Sensitivity Analysis

A sensitivity analysis will be conducted where the FPG and OGTT results will not be counted when evaluating hyperglycemia relapse. The following glycemic outcome definitions will be used:

Diabetes remission	Hyperglycemia relapse
HbA1C <6.5% AND no diabetes drugs for ≥12 weeks AND no relapse	HbA1C ≥6.5% OR Use of diabetes drugs OR Capillary glucose ≥10 mmol/L on ≥50% SMBGs[‡] over 1 week

[‡]SMBG – self-monitoring of blood glucose

Other Outcomes

For all other analyses comparing treatment groups, significance will be assessed using Pearson chi-square test for categorical variables and either two-sample t-test or Wilcoxon test for continuous variables. A linear mixed model will be used to explore changes in measurements for continuous variables (listed below under #1 and 2) as a repeated measurement (MMRM) over time using restricted maximum likelihood. The fixed effects used in the MMRM model will be treatment, time, baseline value (only for the outcomes that includes change or percent change) and the treatment-by-time interaction term and the patient as a random effect.

1. Anthropometric outcomes
   a. Weight
   b. Percent weight loss
   c. Waist circumference
   d. Waist to hip ratio

2. HbA1C

3. Plasma and capillary glucose levels

4. Number and use of specific diabetes medications

5. Physical activity

6. EQ5D

7. Health coaching

All tables are in Appendix A.

8. SAFETY ANALYSIS

All safety variables will be recorded on case report forms and supporting documentation will be obtained. Information on adverse events and pregnancies will be collected as described in the protocol. The investigators will review safety data for this open trial

monthly and more formally after the first 50 participants have completed the trial. Participant safety will be summarized in a series of tables including reported Serious Adverse Events (SAEs), and any serious or non-serious adverse events leading to study drug permanent discontinuation.

9. REPORTING VARIABLES AND P-VALUES

All values will be reported to the first decimal place after the decimal point for means and standard deviations unless otherwise indicated. Relative risks and 95% CIs will be reported to the fourth decimal place. Exact p-values to the fourth decimal place after the decimal point will be reported or the closest p-value will be stated (e.g. <0.00001).