LY3298176 VERSUS DULAGLUTIDE IN TYPE 2 DIABETES MELLITUS TREATMENT (LDT2DM)

Haoran Hu

2019, April

Table of content

1.0 Introduction and Background

Diabetes mellitus is a chronic metabolic disease in which there are high blood glucose levels over a prolonged period[1]. Type 2 diabetes mellitus (T2DM), which is the most common type of diabetes, has become an worldwide epidemic[1]. It occurs when an individual has inadequately low ß-cell function or low sensitivity to insulin[1]. T2DM requires continuous medical treatment to avoid serious complications such as visual impairment and renal failure[2,3]. Historically, various treatments have been developed. Some are for injection, such as insulin, which was developed in the 1920s. Others are for oral use, such as acarbose, which has been on the market for over 20 years[4]. Currently, metformin is one of the most popular treatments. Moreover, some more recently developed treatments, such as dulaglutide, outcompete metformin in efficacy for T2DM treanment[5]. LY3298176, a novel intervention, has been shown to be promising in a phase 2 trial[6,7]. In the phase 2 trial, the posterior mean difference in the changes in glycosylated hemoglobin ($\mathrm{HbA_{1c}}$) from the baseline to the 26-week endpoint was -0.73% comparing LY3298176 verses dulaglutide, with a 80% credible set [-0.95%, -0.52%], and no serious adverse event associated with the treatments occurred throughout the trial[7]. However, the trial does not provide adequate evidence to change clinical practice. Therefore, a decisive phase 3 trial needs to be conducted. This project, LY3298176 versus Dulaglutide in Type 2 Diabetes Mellitus Treatment (LDT2DM) trial, aims to decide if LY3298176 or dulaglutide is more beneficial for T2DM patients, weighing both their efficacy and safety. Dulaglutide will be used as the standard of care in the active control group, since it has demonstrated efficacy and

safety for treatment of T2DM patients[2,5]. Therefore, the clinical question of the trial is: "Is LY3298176 superior to dulaglutide?" This trial will be a randomized, double-blinded, active-controlled phase 3 trial in a two parallel group superiority design. The trial will recruit 18-75 year old T2DM patients who have HbA_{1c} 6.5% - 10.5%, inclusive[6], and the patients will be recruited within the United States. There is no restriction on the race and sex of the patients. The recruited patients will be randomized to either the intervention group or the active control group. The treatment for the intervention group will be once weekly subcutaneous dose of 15mg LY3298176[6], and the treatment for the active control group will be once weekly subcutaneous dose of 1.5mg dulaglutide[6].

2.0 Objectives

i)Primary

The primary outcome will be time to the first hospitalization of the recruited patients because of symptoms related to T2DM in 52 weeks of individual follow-up.

Null hypothesis H_0 : In T2DM patients with HbA_{1c} 6.5% - 10.5%, inclusive, the hazard rate ratio of the first hospitalization because of symptoms related to T2DM is equal to 1 comparing LY3298176 group (patients receiving once weekly subcutaneous dose of 15mg LY3298176) vs. dulaglutide group (patients receiving once weekly subcutaneous dose of 1.5mg dulaglutide) in 52 weeks of individual follow-up.

Alternative hypothesis H_{a1}: In T2DM patients with HbA_{1c} 6.5% - 10.5%, inclusive, the hazard rate ratio of the first hospitalization because of symptoms related to T2DM

is less than 1 comparing LY3298176 group (patients receiving once weekly subcutaneous dose of 15mg LY3298176) vs. dulaglutide group (patients receiving once weekly subcutaneous dose of 1.5mg dulaglutide) in 52 weeks of individual follow-up.

Alternative hypothesis H_{a2}: In T2DM patients with HbA_{1c} 6.5% - 10.5%, inclusive, the hazard rate ratio of the first hospitalization because of symptoms related to T2DM is greater than 1 comparing LY3298176 group(patients receiving once weekly subcutaneous dose of 15mg LY3298176) vs. dulaglutide group(patients receiving once weekly subcutaneous dose of 1.5mg dulaglutide) in 52 weeks of individual follow-up.

The direction of clinical interest is represented by Alternative hypothesis H_{a1}, which is: LY3298176 is superior to dulaglutide in prolonging time to first hospitalization because of symptoms related to T2DM.

ii)Secondary

For simplicity, the word "patients" in this section is equivalent to "T2DM patients with HbA_{1c} 6.5% - 10.5%, inclusive"; the phrase "LY3298176 group" in this section is equivalent to "LY3298176 group (patients receiving once weekly subcutaneous dose of 15mgLY3298176)", and the phrase "dulaglutide group" is equivalent to "dulaglutide group (patients receiving once weekly subcutaneous dose of 1.5mg dulaglutide)".

Secondary outcome 1:the survival time of the patients in 52 weeks of individual follow-up.

Null hypothesis H_0:The hazard rate ratio of death is equal to 1 comparing LY3298176 group vs. dulaglutide group in 52 weeks of individual follow-up.

Alternative hypothesis H_{a1}: The hazard rate ratio of death is less than 1 comparing LY3298176 group vs. dulaglutide group in 52 weeks of individual follow-up.

Alternative hypothesis H_{a2}: The hazard rate ratio of death is greater than 1 comparing LY3298176 group vs. dulaglutide group in 52 weeks of individual follow-up.

Secondary outcome 2: the change in HbA_{1c} of the patients from the baseline to the endpoint of 52 weeks of individual follow-up.

Null hypothesis H_0: LY3298176 group and dulaglutide group do not differ in the average change in HbA_{1c} in 52 weeks of individual follow-up.

Alternative hypothesis H_{a1}: Patients in LY3298176 group has a greater average reduction in HbA_{1c} than patients in dulaglutide group in 52 weeks of follow-up.

Alternative hypothesis H_{a2}: Patients in dulaglutide group has a greater average reduction in HbA_{1c} than patients in LY3298176 group in 52 weeks of follow-up.

Secondary outcome 3: the change in fasting blood glucose level of the patients from the baseline to the endpoint of 52 weeks of individual follow-up.

Null hypothesis H_0: LY3298176 group and dulaglutide group do not differ in the average change in fasting blood glucose level in 52 weeks of individual follow-up.

Alternative hypothesis H_{a1}: Patients in LY3298176 group has a greater average reduction in fasting blood glucose level than patients in dulaglutide group in 52 weeks of individual follow-up.

Alternative hypothesis H_{a2}: Patients in dulaglutide group has a greater average

reduction in fasting blood glucose level than patients in LY3298176 group in 52 weeks of individual follow-up.

iii)Safety

1) Hypoglycemia. This will be a categorical outcome: whether a patient experiences hypoglycemia or not. This will be measured by self-monitoring of blood glucose (SMBG). The instruments needed include: lancets, a lancet device, reagent strips, a blood glucose meter[8], and appropriate worksheets and computers that are used to record the test results. The instruments will be provided to the patients at the time of randomization. The patients will be asked to perform at least two fasting SMBG tests each week[8], and they will be suggested to perform the fasting SMBG tests on each Tuesday, Thursday, and Saturday. The clinical coordinators will collect the data at each patient visit (every 8 weeks, according to the schedule in section 4.0). Patients having glucose levels below 3.9 mmol/L (70 mg/dL) will be classified as experiencing hypoglycemia[9].

2) Gastrointestinal side effects. The data type will be continuous. This will be measured by Gastrointestinal Clinical Symptom Index (GCSI), a validated questionnaire that will give an overall score[10], reflecting the severity of gastroparesis symptoms. Besides the GCSI questionnaires, the needed instruments also include: appropriate worksheets and computers that are used to record the test results. A patient will be asked to fill out the questionnaire during each visit (every 8 weeks, according to the schedule in section 4.0). Once the patient finishs the questionnaire, the response

will be collected by the clinical coordinators.

3) Possible development of pancreatitis. This will be a categorical outcome, either displaying a sign of pancreatitis or not. The needed instruments includes: vacutainer needles, vacutainer tubes, a clinical laboratory which can check digestive enzyme level at the site, and appropriate worksheets and computers that are used to record the results. At each visit of the patient (every 8 weeks, according to the schedule in section 4.0), the clinicians will collect a blood sample in a vacutainer tube, and send it to the clinical laboratory of the hospital to check digestive enzyme levels. If there is at least threefold increase in pancreatic enzymes amylase and lipase compared to normal level, then the patient will be considered possible to develop pancreatitis[5].

3.0 Trial Design

i)RCT Features

The proposed trial will be a prospective, interventional, randomized, double-blinded, and active-controlled phase 3 trial. Besides, the trial will have complete follow-up, and intent-to-treat analysis will be used in this trial. Details of how the trial will incorporate and achieve each of these features are as follows.

1) The trial will be prospective, since the patients will be recruited at baseline and will be followed for a period of time. 2) The trial will involve interventions, including LY3298176 treatment and dulaglutide treatment. 3) There will be a control group in the trial. The dulaglutide treatment group will be an active control group. 4) The patients will be stratified by site and randomized by randomly permuted blocks into

the two intervention groups, resulting in roughly the same number of patients in each group. 5) The trial will be double blinded. The patient will receive two sets of injection containers. If the patient is in LY3298176 group, one set of the containers will contain active LY3298176, and the other set will contain placebo dulaglutide (saline). If the patient is in dulaglutide group, one set will contain placebo LY3298176 (saline), and the other set will contain active dulaglutide. The patient will fill a syringe with one dose of injection from each set of containers, and then give a single subcutaneous injection to him/herself. Then, neither the patient nor the clinicians would know which treatment is given to the patients. 6) Intent-to-treat analysis will be used. Every randomized patient will be analyzed in the group that he/she is randomized to. 7) The trial will have complete follow-up. The eligibility criteria ensures that only patients that are likely to complete the trial will be enrolled in the trial. The goal is to have less than 1% loss to follow-up. This target includes withdrawals of consent.

ii)Blinding

The trial will be double blinded. The clinicians (and their staff, including the nurses, outcome assessors, etc.), the site coordinators, and patients will be blinded to the maximum extent possible throughout the trial, and they will not know the interventions to which patients are assigned. The steps taken to ensure blinding are:

Step 1. Each recruited patient will be randomly assigned to either the LY3298176 treatment group (the intervention group) or the dulaglutide treatment group (the active control group). Neither the patient nor the clinicians (and their staff) will know which

group the patient is actually assigned to.

Step 2. Before the injections are distributed to the patients, they must be kept in a place with limited access. Only the research coordinators who are responsible for distributing the injections will have access to them.

Step 3. The injections will be distributed to each randomized patient. Each randomized patient will receive two sets of injection containers with injections in them. The first set of containers are either 15mg LY3298176 injection containers, or identical appearing placebo (saline) injection containers. The second set of containers are either 1.5mg dulaglutide injection containers, or identical appearing placebo (saline) injection containers. If the patient is assigned to the LY3298176 treatment group, he/she will receive LY3298176 and placebo dulaglutide. If the patient is assigned to the dulaglutide group, he/she will receive dulaglutide and placebo LY3298176.

Step 4. The patient will fill a syringe with one dose of injection from each set of containers they receive, one after another, and then give a single subcutaneous injection to him/herself. The injection will be given to him/herself once a week.

iii)Randomization

Stratification will be applied in the randomization process. Site will be the only stratification variable in this trial. The reason why the randomization needs to be stratified by site is that baseline covariates and treatment effects typically vary considerably for T2DM patients in different sites[12], and stratifying by site can prevent these variations from affecting the evaluation of the treatment effect. Stratifying on

other variables in this trial is unnecessary, and may cause over-stratification. Then, each site will be a stratum, and within each stratum, patients will be randomized to either LY3298176 treatment group or dulaglutide treatment group using randomly permuted blocks. Within each stratum, the blocks will have block sizes of 4, 6, and 8 with pre-specified proportions of 50%, 40%, and 10%, respectively, and block size will vary randomly within these given sizes. The "randomization.com" will be used by data coordinators to generate one randomization list showing treatment assignments for each stratum, using different seeds for different strata. This blocking scheme guarantees exact balance at the end of every block, and make it very hard to predict the treatment arm for a patient. The chosen seeds will be recorded and will be accessible only to authorized data coordinators, so that the data coordinators can reproduce the random assignment scheme or extend the list for more cases when this is needed.

iv)Inclusion and Exclusion Criteria

Inclusion criteria: 1)All sexes are eligible for study. The sample should model the total population, and the medication is suitable for all sexes. 2)All races are eligible for study. The sample should model the total population. 3)Patient is 18-75 year old. Clinical trials are typically conducted among adults (≥18 years old), and should exclude elderly people (>75 years old) who are getting increasingly frail[11]. 4) Patient has T2DM based on the disease diagnostic criteria (refer to the World Health Organization's [WHO] Classification of Diabetes)[5]. 5)Patient has HbA_{1c} 6.5% - 10.5%, inclusive[6].This is the common range of HbA_{1c} for T2DM patients. 6)Patient

has easy access to hospitals that are able to treat symptoms related to T2DM. The trial requires frequent visits to the hospitals. 7) Approval from health care provider to stop current treatment and use treatments in the trial as substitutes. This is to ensure that it is not likely to be harmful for the patient to stop the current treatment and use a substitute treatment. 8)Patient is capable and willing to perform self-monitored blood glucose testing[5]. The self-monitored blood glucose (SMBG) tests should be well-performed, as the test results will be an important part of the safety outcomes.

Exclusion criteria: 1)Patient is unable to provide informed consent. Clinical trials require informed consent from patients. 2)Patient has active psychosis, a substance abuse problem, or received psychiatric care in the past 6 months[12]. These conditions are potential causes of loss to follow-up. 3)Patient has type 1 diabetes mellitus. Treatments in this trial are not suitable for management of type 1 diabetes mellitus[2]. 4)Patient has a problem with the liver or pancreas[5]. This is to prevent serious adverse effects such as pancreatitis and liver injuries[13]. 5)Patient has a blood disorder that would interfere with blood sample measurements in the trial process[5].This is to avoid difficulties for blood sample collection and assessment because of blood disorders. 6) Patient has a cognitive disorder. Cognitive disorder may cause difficulties for patients to follow the instructions given by research coordinators.

v) Enrolling Centers

The types of enrolling center the trial will include are: major medical centers and hospital clinics.

vi) Data Coordination and Trial Management

There will be a Data Coordinating Center (DCC) for the trial. The DCC will be responsible for maintaining the data management system[14], which will collect all the data in the trial, and it will also be responsible for performing data analysis. It will develop statistical designs and randomization schemes before the trial. In the on-going process of the trial, it will perform interim analyses, keep monitoring patients' safety data, and keep in close collaboration with the Data and Safety Monitoring Board (DSMB). It will also be responsible for backing up the data and keeping all the data secure[14]. There will be experienced statisticians, data managers and data coordinators in the DCC to ensure that this work will be done properly.

There will also be appropriate Clinical Trial Management (CTM) resources in the trial. The budget of the trial will be well-planned. For the CTM to be at a level appropriate for this trial, there will be experienced trial coordinators that are in charge of ensuring that the enrolled patients meet the eligibility criteria, and making sure that the enrolled patients come for their scheduled visits on time[14]. The CTM trial coordinators are also responsible for encouraging patients to follow the instructions, such as performing SMBG tests on time, to the maximum extent possible. In addition, the CTM trial coordinators will track adverse events and report the adverse events to the DSMB[14].

vii) Sidedness of Test

A two sided test will be utilized for assessing the primary outcome, with symmetric allocation of α. Neither the LY3298176 treatment nor the dulaglutide treatment will

be presupposed to be superior in this superiority design trial, and thus a two-sided test will be used for assessing the primary outcome.

4.0 Data Collection and Patient Follow-up

i) Outcome Details

Primary outcome:

The primary outcome variable will be the time from the baseline to the first hospitalization because of symptoms related to T2DM. This will be a time to event outcome variable. The instruments that will be used in constructing this outcome variable are worksheets and several computers at each site that enable the research coordinators to enter the data into the data management system of this trial. The instruments can accurately reflect the primary outcome and they are validated instruments because they enable the researchers to accurately record and maintain these time to event outcome data. At the patient's each visit (according to the schedule in section 4.0), the clinical coordinators will inquire about the patient's hospitalization in the past eight weeks, and record the response. If a patient is hospitalized because of symptoms related to T2DM, the time from baseline to the first hospitalization will be collected and recorded on an appropriate worksheet by a clinical coordinator at the site and will be entered into the data management system by a data coordinator as the primary outcome variable for the patient. Otherwise, time from baseline to the time of the censoring of the patient will be collected and recorded on an appropriate worksheet by a clinical coordinator at the site and the censored data will be entered into the data

management system by a data coordinator as the primary outcome variable for the patient. Then, the primary outcome variable is constructed as a time to event outcome variable.

Secondary outcome 1:

The first secondary outcome variable is the survival time of the patients in 52 weeks of individual follow-up. This will be a time to event outcome variable. The needed instruments are computers that enable the research coordinators to enter the data into the data management system. The instruments can accurately reflect this outcome and they are validated because they enable the researchers to accurately record and maintain the patients' survival time data. At each site, the data coordinators will contact the clinical coordinators to check a patient's survival state (live or death) within one week after each scheduled dates of visits (as scheduled in section 4.0). If a patient dies for any reason within the follow-up period, the time from the baseline to the time the patient dies will be collected and entered into the data management system by the data coordinators as the survival time. Otherwise, time from the baseline to time of the censoring of the patient will be entered into the data management system as censored data by the data coordinators. These recorded data will be treated as the time to event outcome variable, and this outcome variable is constructed.

Secondary outcome 2:

The second secondary outcome is the change in HbA_{1c} of the patients from the baseline to the endpoint of 52 weeks of individual follow-up. This is a continuous outcome variable. The instruments that will be used to construct this variable includes:

finger sticks that are used to obtain venous blood sample, Quo-Lab HbA1c Analyzers[15] that are used to analyze HbA_{1c} level in the blood sample, cartridges that are used to insert the blood sample into the analyzer, and worksheets and computers that are used to record the data. The instrument uses boronate affinity method[15], which can accurately reflect the HbA_{1c} level. It is a validated instrument, with imprecision less than 3%[15]. To perform the HbA_{1c} test, the clinician administering the test will first obtain blood sample (at least 4μl) from the patient. Then, he/she will insert a cartridge into the HbA1c analyzer and the blood sample will be moved into the cartridge for analysis. The clinicians will collect the results (HbA_{1c} levels) and record the results on an appropriate worksheet, and the data coordinators will collect the data from the clinicians and enter the data into the data management system once a day. For each patient, HbA_{1c} will be tested at the baseline and at the 52 week endpoint. The tests will be carried out at the sites. By subtracting the HbA_{1c} level at the baseline from the HbA_{1c} level measured at the 52-week endpoint, the change in HbA_{1c} in the follow up period for the patient is obtained, and the outcome variable is constructed.

Secondary outcome 3:

The third secondary outcome is the change in fasting blood glucose level of the patients from baseline to the endpoint of 52 weeks of individual follow-up. This is a continuous outcome variable. The instruments that will be used include: lancets, lancet devices, reagent strips, blood glucose meters[9], and worksheets and computers that are used to record the data. The blood glucose meter can measure an electric charge which is produced by glucose-reagent reaction, and thus it can accurately reflect blood

glucose level[16]. These are accurate instruments that are widely used in hospitals[16].To perform the fasting blood glucose level test, the clinicians administering the test should ask the patient to have an overnight fast in advance. When the patient visits the site, the clinicians insert a reagent strip into the reflectance photometer, prick the end of a finger of the patient with the lancet device, and apply the blood to the strip. When the meter displays the result, the clinicians will collect the result (fasting blood glucose level), and record it on an appropriate worksheet. The data coordinators will collect the data from the clinicians and enter the data into the data management system once a day. Each patient will be required to take the test at the baseline and at the 52-week endpoint. The tests will be carried out at the sites. By subtracting the fasting blood glucose level at the baseline from the blood glucose level at the 52-week endpoint, the change in fasting blood glucose is obtained, and the outcome variable is constructed.

ii) Data Collection Mechanism

A web-based data management system with Electronic Case Report Forms (eCRFs) will be used for the trial. Typically, the information collected in the trial will first be recorded on an appropriate worksheet by trial coordinators. Then, the information will be entered into a specific eCRF on the data management system by data coordinators. The eCRFs should be submitted to the DCC within one week after the information is collected. All the collected data will be backed-up.

iii) Schedule of Visits

Table [1] Visit Schedule for the LDT2DM Trial (Page 1)										
	Screening Period		**Double-Blinded Treatment Period**							
Milestone		RD.	Base.							EOF
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10
Day	d-14 to d-8	d-7	d1	d57	d113	d169	d225	d281	d337	d365
Week	Wk -2	Wk -1	Wk0	Wk8	Wk 16	Wk 24	Wk 32	Wk 40	Wk 48	Wk 52
Screening/Base.										
Informed Consent	X									
Inclusion/Exclusion	X									
Randomization		X								
Treatment										
Dispense injections(and instruments)			X							
Injection Training			X							
Safety Assessments										
BP and PR			X	X	X	X	X	X	X	X
Electrocardiogram			X	X	X	X	X	X	X	X
Body weight			X	X	X	X	X	X	X	X
Dispense SMBG instruments		X								
SMBG worksheet collection			X	X	X	X	X	X	X	X
GCSI			X	X	X	X	X	X	X	X

Table [1] Visit Schedule for the LDT2DM Trial (Page 2)										
	Screening Period		**Double-Blinded Treatment Period**							
Milestone		RD.	Base.							EOF
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10
Day	d-14 to d-8	d-7	d1	d57	d113	d169	d225	d281	d337	d365
Week	Wk -2	Wk -1	Wk0	Wk8	Wk 16	Wk 24	Wk 32	Wk 40	Wk 48	Wk 52
pancreatitis test			X	X	X	X	X	X	X	X
Primary outcome Assessment										
Time to 1st hosp.			X	X	X	X	X	X	X	X
Secondary outcome Assessment										
Survival time			X	X	X	X	X	X	X	X
HbA1c			X							X
Fasting blood glucose level			X							X

•RD. = Randomization; Base. = Baseline; EOF = End of follow-up

• BP = Blood pressure; PR = Pulse rate; SMBG = Self-monitored blood glucose; GCSI = Gastrointestinal Clinical Symptom Index; 1st hosp. = the first hospitalization; HbA1c = hemoglobin A1c

iv) Trial Timeline

The individual follow-up period will be approximately 1 year (52 weeks). As the trial may need to enroll a large number of patients, the accrual time will be 2 years. Thus, the total follow-up time will be 3 years. The length of startup period, total follow-up time, time for data cleaning, and time for statistical analysis are shown in figure 1.

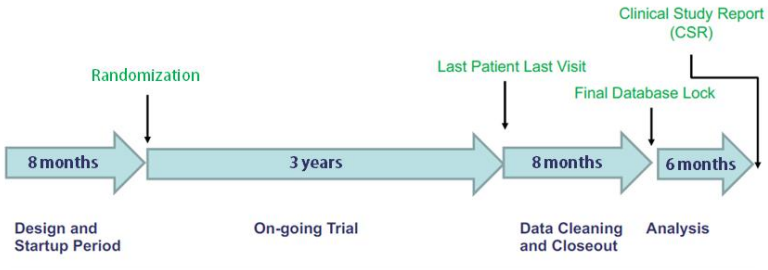

Figure 1: Trial timeline

5.0 Statistical Considerations

i) Type of Outcome

The primary outcome will be a time to event outcome. The statistical design is superiority. The two alternative hypotheses are expressed in terms of hazard rate ratio, as shown in section 2.0, and the statistical test will be two-sided log rank test, with experiment wide type I error rate $\alpha = 0.05$ and with symmetric allocation of α.

ii) Power Calculation: Unadjusted and Adjusted Effect Size

The unadjusted hazard rate for the first hospitalization because of T2BM in the control group is estimated to be 0.19 per patient-year, or 0.0037 per patient-week[17]. As the information needed for estimating the effect size is not available in the corresponding phase 2 trial, information provided by other studies was used to determine the least clinically meaningful effect size. Studies show that there are plenty of novel interventions for T2BM, with relatively large effect size[18], and for effective novel interventions, the effect sizes are typically larger than 20%[19]. To avoid the situation where a trivial, clinically irrelevant effect is statistically significant, the least clinically meaningful effect size should not be too small. On the other hand, to avoid the

situation where the trial fails to detect a meaningful effect, the effect size should not be set too large. In this consideration, it is reasonable to set the least clinically meaningful effect size to 20%. An estimated 2% of the patients randomized to LY3298176 group will switch to dulaglutide group, and an estimated 2% of the patients randomized to dulaglutide group will switch to LT3298176 group, as it is not easy to crossover in this trial. Besides, an estimated additional 5% of the patients randomized to each group will be noncompliant, as the injection schedule might be difficult for some patients to follow. The adjusted effect size is 18.1%. The calculations to get the adjusted effect size are given in the appendix. With noncompliance and crossovers, the effect size tends to get smaller, and if the unadjusted effect size is used in calculating the sample size, the sample size tends to be underestimated and the trial will be underpowered. Thus, the adjusted effect size is used in place of unadjusted effect size as it accounts for noncompliance and crossover.

iii) Sample size

The sample size is calculated using the adjusted effect size, and an interim analysis design is taken into account when calculating the sample size. With significant level 0.05, desired power 0.80, adjusted hazard rate of first hospitalization 0.188 / pt-year for the control group, adjusted hazard rate of first hospitalization 0.154 / pt-year for the intervention group, individual follow-up 1 year, and four interim looks equally spaced by information (fraction of information: 0.2, 0.4, 0.6, 0.8, respectively, for each interim look), the targeted sample size can be calculated using PASS, and the output is in Table 2.

Table 2: Sample size calculated using Group Sequential procedures (using PASS)

Group-Sequential Logrank Tests

Numeric Results for Two-Sided Logrank Test (Assuming Exponential Survival)

Power	Total Sample Size (N)	Total Required Events	Alpha	Beta	Proportion Surv. (S1)	Proportion Surv. (S2)	Hazard Ratio
0.800040	5139	807.1	0.050000	0.199960	0.8286	0.8573	0.8190

The sample size is calculated using group sequential procedure, under an exponential survival assumption. The output shows that the total sample size needed for the trial is 5139, with approximately 2570 patients in each treatment group.

iv) Sensitivity Analysis

Table 3 shows how changes in effect size affect the needed sample size.

Table 3: Sample sizes needed for different effect sizes (computed by PASS)

Sample size per arm with Power = 0.8			
	HR = 0.819	HR = 0.840	HR = 0.860
2 year (104 weeks) accrual and 1 year (52 weeks) additional follow-up	2570	3334	4411

Given the unadjusted least clinically meaningful effect size, if the adjusted least clinically meaningful effect size is smaller than the adjusted effect size that is used to calculate the sample size for this trial for some reason, the needed sample size should increase, as shown in table 3. If the adjusted hazard ratio is 0.840, the sample size needed will increase to 3334, and if the adjusted hazard ratio is 0.860, the sample size needed will increase to 4411. Some possible reasons that may cause the actual adjusted

effect size to be less than the adjusted effect size used for this trial includes: more crossovers than expected, more noncompliant patients than expected, etc. Thus, if the actual adjusted effect size is smaller than the estimated adjusted effect size, which is 18.1%, the sample size would be underestimated and the trial would be underpowered.

v) Interim Analysis Plan

Table 4: Interim analysis plan (Calculated by PASS)

Details when Spending = O'Brien-Fleming, N = 5139, d = 807, S1 = 0.8286, S2 = 0.8573

Look	Info	Lower Bndry	Upper Bndry	Nominal Alpha	Inc Alpha	Total Alpha	Inc Power	Total Power
1	161	-4.87688	4.87688	0.000001	0.000001	0.000001	0.000154	0.000154
2	323	-3.35695	3.35695	0.000788	0.000787	0.000788	0.058859	0.059013
3	484	-2.68026	2.68026	0.007357	0.006828	0.007616	0.257526	0.316540
4	646	-2.28979	2.28979	0.022034	0.016807	0.024424	0.288912	0.605452
5	807	-2.03100	2.03100	0.042255	0.025576	0.050000	0.194588	0.800040

The interim analysis plan is displayed in table 4. The time of each interim look is respectively the time when 1/5, 2/5, 3/5, and 4/5 of the total expected number of events, which are the first hospitalizations caused by T2DM, is observed. Specifically, when 161, 323, 484, and 646 events are observed, interim looks will be taken. At each look, the z-score for the difference between the two groups will be computed, and if it lies outside the boundaries, the statistical early stopping rule is achieved. Corrections are made for multiple tests to control the experiment wide Type I error rate to be 0.05, and error spending approach (using alpha spending functions) is used for this purpose.

As shown in table 4, there will be 4 interim analyses. From the first interim look to the fourth interim look, the lower stopping boundaries are respectively -4.877 (z-score: -4.877, p-value: 1×10^{-6}), -3.357 (z-score: -3.357, p-value: 7.87×10^{-4}), -2.680 (z-score: -2.680, p-value: 6.83×10^{-3}), and -2.290 (z-score: -2.290, p-value:

1.68×10^{-2}), and the upper stopping boundary are respectively -4.877(z-score: -4.877, p-value: 1×10^{-6}), -3.357 (z-score: -3.357, p-value: 7.87×10^{-4}), -2.680 (z-score: -2.680, p-value: 6.83×10^{-3}), and -2.290 (z-score: -2.290, p-value: 1.68×10^{-2}).

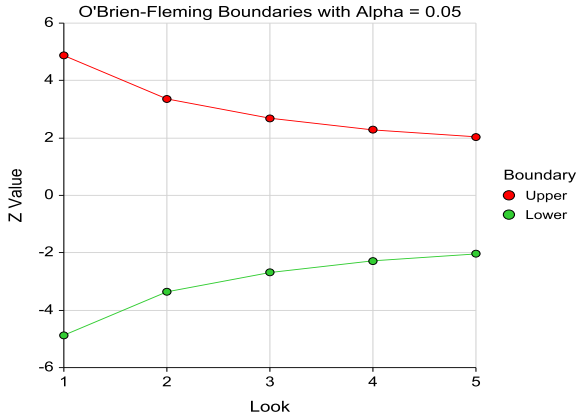

Figure 2: Interim stopping boundaries (computed by PASS)

Figure 2 shows the interim boundaries for each look. If the computed z value for a look is between these boundaries, the trial should continue. Otherwise, if the computed z value for a look crosses the upper bound, then there is emerging evidence suggesting LY3298176, the new intervention, is superior; if the computed z value for a look crosses the lower bound, then there is emerging evidence suggesting dulaglutide is superior. In this case, the trial can be stopped, depending on other considerations. The stopping bounds are symmetric, because the trial is in superiority design with active control, and tests are two sided with symmetric allocations of alpha.

6.0 Safety Considerations

i) Measurement of the safety outcomes

Safety outcome 1: Hypoglycemia

This will be a categorical outcome: whether a patient experiences hypoglycemia or not.

The instruments, which are listed in section 2.0, will be provided to the patients. The patients will be asked to perform at least two fasting SMBG tests each week at home[8], and they will be suggested to perform the fasting SMBG tests on each Tuesday, Thursday, and Saturday. To perform the fasting SMBG test, the patient will have an overnight fast in advance. When performing the test, he/she will first insert a reagent strip into the reflectance photometer, and then prick the end of a finger with the lancet device, and apply the blood to the reagent strip. When the meter displays the result, the patient will record the result on a worksheet. The worksheets will be collected by a clinical coordinator when he/she visits the site (as scheduled in section 4.0), and data coordinators will collect the worksheets from the clinical coordinators and enter the data into the data management system once a week. Patients having glucose levels below 3.9 mmol/L in any one test will be classified as experiencing hypoglycemia[9].

Safety outcome 2: Gastrointestinal side effects

This outcome will be measured by Gastrointestinal Clinical Symptom Index (GCSI), a validated questionnaire that will give an overall score[10] reflecting the severity of gastroparesis symptoms. The score ranges from 0-5, with higher scores reflecting more sever conditions[10]. This will be recorded as continuous data. Each patient will be asked to fill out the questionnaire during each of his/her visits. Once the questionnaire is finished, it will be collected by a clinical coordinator. Then, the clinical coordinator will calculate the GCSI and record the result on a worksheet. The data coordinators will collect the worksheets from the clinical coordinators and enter the data into the data management system once a week.

Safety outcome 3: Possible development of pancreatitis

For each patient, during each of his/her visits, the clinicians will collect a blood sample of the patient in a vacutainer tube, and send it to the clinical laboratory of the hospital to check digestive enzyme levels. If there is at least threefold increase in pancreatic enzymes amylase and lipase compared to normal level, then the development of pancreatitis in the patient will be considered possible[5]. The clinical coordinators will record the result (whether or not the development of pancreatitis is possible) on worksheets, and the data coordinators will collect the worksheets and enter the information on them into the data management system once a week.

ii) Reasons for Measuring these Key Safety Outcomes

Patients' safety will be the first priority. Although no serious adverse effect occurred in the phase 2 trial, these three safety outcomes still need to be monitored in the proposed phase 3 trial as the phase 3 trial will have a longer individual follow-up period with more patients. The outcomes are also important for evaluating the safety of LY3298176. The specific reasons for measuring these three safety outcomes are:

1) Although T2DM may be protective against hypoglycemia[20], many previous medications for treating T2DM have side effects of triggering hypoglycemia[21], which may lead to serious symptoms such as unconsciousness[9]. Therefore, to evaluate the safety of LY3298176, the risk of hypoglycemia should be monitored in the trial.

2) For previous glucagon-like peptide-1 (GLP-1) analogue medications of T2DM, gastrointestinal adverse effects, including nausea and vomiting, are the most common adverse effects[21]. LY3298176 is also a GLP-1 analogue analogue[7], and it may also

trigger these adverse effects. These adverse effects may interfere with patients' daily lives. Hence, severity of gastrointestinal symptoms need to be measured in the trial.

3) T2DM patients have increased risks of acute pancreatitis[22,23], which is a serious inflammation. Besides, pancreatitis is also considered as a side effect of other GLP-1 analogue medications such as dulaglutide[13].Thus, it is important to monitor whether or not there is a sign of pancreatitis for each patient.

iii) Other safety outcomes

1)Vital signs[7]. Blood pressure (BP) and pulse rate (PR) will be monitored throughout the trial, using standardized equipment and according to the schedule in section 4.0.

2) Electrocardiograms[7]. Electrocardiograms will be measured using standardized equipment and according to the schedule in section 4.0.

3) Body weight[7]. Body weight will be measured by a weighing scale, according to the schedule in section 4.0.

7.0 Limitations and late-breaking problems

One limitation of study is that only 18-75 year old patients will be enrolled. Thus, the efficacy and safety of LY3298176 for patients younger than 18 years old or older than 75 years old will be uncertain. In addition, the 52-week individual follow up will not be able to evaluate the safety and efficacy of LY3298176 for longer term treatments. Moreover, the trial population may not be large enough to detect rare adverse effects.

In future revisions, more secondary outcomes and safety outcomes should be identified to help better evaluate the efficacy and safety of LY3298176.

8.0 References

1. Stumvoll M, Goldstein BJ, Haeften TWV. Type 2 diabetes: principles of pathogenesis and therapy. Lancet 2005;365:1333-46.

2. Kalyani RR, Cannon CP, Cherrington AL, et al. Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018;41:S1-S156.

3. Nathan DM. Long-Term Complications of Diabetes Mellitus. N Engl J Med1993;328:1676-85.

4. Peñalver JJM, Timón IM, Collantes CS, Gómez FJDC. Update on the tr eatment of type 2 diabetes mellitus. World J Diabetes 2016;7:354-95.

5. Umpierrez G, Povedano ST, Manghi FP, Shurzinske L, Pechtner V. Effi cacy and Safety of Dulaglutide Monotherapy Versus Metformin in Type 2 Diabetes in a Randomized Controlled Trial (AWARD-3). Diabetes C are 2014;37:2168–76.

6. Coskun T, Sloop KW, Loghin C, et al. LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: From discovery to clinical proof of concept. Molecular Metabolism 201 8;18:3-14.

7. Frias JP, Nauck MA, Van J, et al. Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 dia

betes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. THE LANCET 2018;392:17-23.

8. Benjamin EM. Self-Monitoring of Blood Glucose: The Basics. Clinical D iabetes 2002;20: 45-47.

9. The National Institute of Health. Low Blood Glucose (Hypoglycemia) [In ternet]. NIDDK. 2016 [Cited 2019 March 22];Available from:https://www. niddk.nih.gov/health-information/diabetes/overview/preventing-problems/low-blood-glucose-hypoglycemia

10. Revicki DA, Rentz AM, Dubois D, et al. Gastroparesis Cardinal Sympto m Index (GCSI): development and validation of a patient reported assess ment of severity of gastroparesis symptoms. Qual Life Res2004;13:833-4 4.

11. Jiwa M, Gudes O, Varhol R, Mullan N. Impact of geography on the co ntrol of type 2 diabetes mellitus: a review of geocoded clinical data fro m general practice. BMJ Open 2015; 5(12): e009504.

12. Johnson EJ, Niles BL, Mori DL. Targeted Recruitment of Adults With Type 2 Diabetes for a Physical Activity Intervention. Diabetes Spectrum 2015; 28:99-105.

13. The National Institute of Health. DULAGLUTIDE [Internet]. NIH. 2018 [Cited 2019 April 17];Available from: https://livertox.nih.gov/Dulaglutide.htm

14. UCSF. Clinical Study Management [Internet]. UCSF. 2017 [cited 2019 Apr 23];Available from: https://hub.ucsf.edu/clinical-study-management

15. Heinemann L, Freckmann G. Quality of HbA1c Measurement in thePractice: The German Perspective. Journal of Diabetes Science and Technology2015;9(3):687-95.

16. Lee M, editor. Basic Skills in Interpreting Laboratory Data. Downers Grove, IL, USA: ASPH; 2013

17. Khalid JM, Raluy-Callado M, Curtis BH, et al. Rates and risk of hospitalisation among patients with type 2 diabetes: retrospective cohort study using the UK General Practice Research Database linked to English Hospital Episode Statistics. Int J ClinPract 2014;68(1):40-8

18. Seewoodhary J, Bain SC. Novel treatments for type 2 diabetes. Br J Gen Pract 2011;61(582):5-6

19. Nyström T, Bodegard J, Nathanson D, et al. Novel oral glucose-lowering drugs are associated with lower risk of all-cause mortality, cardiovascular

events and severe hypoglycaemia compared with insulin in patients with type 2 diabetes. Diabetes Obes Metab 2017;19(6):831-41

20. Zammitt NN, Frier BM.Hypoglycemia in type 2 diabetes: pathophysiology, frequency, and effects of different treatment modalities. Diabetes Care 2005;28(12):2948-61.

21. Prasad-Reddy L, Isaacs D. A clinical review of GLP-1 receptor agonists: efficacy and safety in diabetes and beyond. Drug Context 2015;doi: 10.7573/dic.212283.

22. Gonzalez-Perez A, Schlienger RG, Rodr ́guez LAG. Acute Pancreatitis in Association With Type 2 Diabetes and Antidiabetic Drugs. Diabetes Care 2010;33(12):2580-85.

23. Aghani E. Acute Pancreatitis.Pancreapedia: Exocrine Pancreas Knowledge Base2014;DOI: 10.3998/panc.2014.14