Predicting Long-Term Outcome Risk with Tirzepatide: A Post-Hoc Analysis of SURMOUNT-1
2022-11193

Tirzepatide (LY3298176)

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Protocol Electronically Signed and Approved by Lilly: approval date provided

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5. Background and Rationale

Obesity is a chronic, relapsing, progressive disease. According to the current epidemiological trends reported by the World Obesity Federation, obesity is estimated to affect a population of over 1 billion by 2025.[1] Overweight and obesity are characterized by abnormal or excessive accumulation of fat leading to impaired health.[2] Energy imbalances (calories consumed versus calories spent), medical conditions (Prader-Willi syndrome, Cushing's syndrome), and certain medicines (anti-depressants and anti-psychotics) are known to contribute to overweight or obesity. In addition, risk factors such as age, family history, genetics, ethnicity, and unhealthy lifestyle contribute to obesity.[3]

Obesity is associated with significant risk of morbidity and mortality. The major comorbidities associated with obesity include type 2 diabetes mellitus, cardiovascular disease, dyslipidemia, hypertension, chronic obstructive pulmonary disease, obstructive sleep apnea, certain types of cancer, gastroesophageal reflux disease, arthritis, steatohepatitis, polycystic ovary syndrome, and infertility.[2, 4-7] Evidence suggests that effective weight loss interventions significantly reduce obesity-related morbidity and may reduce mortality.[8] In the US, the Endocrine Society recommends that diet, physical activity, and behavioral modifications be part of all obesity management approaches for patients with body mass index (BMI) ≥25 kg/m^2.[9] Interventions such as pharmacotherapy are recommended in patients with BMI ≥27 kg/m^2 with at least one weight-related comorbidity or BMI over 30 kg/m^2 with or without comorbidities.[9]

Tirzepatide (LY3298176; TZP) is a novel glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist that induces substantial reduction in body weight and improvement in cardiometabolic risk factors.[10] SURMOUNT-1 is the first global registration trial with available data at this time evaluating TZP for the treatment of people with overweight or obesity with topline results released April, 2022. In the absence of trials evaluating the impact of TZP on long-term outcomes, the goal of this study is to model the change in risk for long-term outcomes from baseline to 72 weeks using SURMOUNT-1 trial data.

Atherosclerotic Cardiovascular Disease (ASCVD) will be predicted using a risk engine developed in 2013 by the American College of Cardiology/American Heart Association (ACC/AHA).[11-12] The model was developed using several pooled cohorts, that included African American and white participants. The model inputs are age, total cholesterol, high density lipoprotein (HDL), systolic blood pressure, treatment for blood pressure, diabetes mellitus, and current smoking status. This model was selected over the Framingham model due to its broader generalizability across populations. Type 2 diabetes will be predicted using the Cardiometabolic Disease Staging (CMDS) model, which uses the following characteristics to estimate the 10-year risk for developing type 2 diabetes: age, sex, race, BMI, triglycerides, HDL, blood pressure, and blood glucose.[13-14] This model was chosen because it was developed in a more generalizable population and outperforms the Framingham model.[13]

6. Objectives

6.1 Primary Objective

To describe and compare the change from baseline predicted risk of long-term outcomes (listed below) between tirzepatide and placebo at 72 weeks among people with overweight or obesity using SURMOUNT-1 trial data.

- Atherosclerotic Cardiovascular Disease
- Type 2 diabetes

6.2 Secondary Objective

To describe and compare the predicted risk of long-term outcomes (listed below) at baseline, 24 weeks, and 72 weeks between tirzepatide and placebo among people with overweight or obesity using SURMOUNT-1 trial data

- Atherosclerotic Cardiovascular Disease
- Type 2 diabetes

7. Research Design

7.1 Summary of Research Design

This will be a post-hoc analysis of SURMOUNT-1 individual patient level data comparing the change in risk for long-term outcomes from baseline to 72 weeks between TZP groups and placebo. Risk will be evaluated at baseline, 24 weeks, and 72 weeks. The risk for outcomes will be modelled using risk engines specified in section 9.1.

7.2 Data Source (applicable to the Secondary Use of Data)

Individual patient level data from the phase 3 clinical trial (NCT04184622) evaluating the safety and efficacy of Tirzepatide for people with overweight or obesity (SURMOUNT-1) will be used. Adverse events will not be used as model inputs, though for a sensitivity analysis of the ACC/AHA risk engine, CVD events will be used as an exclusion criterion post-baseline (please see section 9.6 for details). No adverse events will be used to validate the models (e.g. as an outcome).

7.3 Study Population

7.3.1 Selection Criteria

The Efficacy Analysis Set (EAS) from SURMOUNT-1 will be used for this study. EAS includes all 2539 participant data obtained during treatment period from the modified intent-to-treat (mITT, all randomized participants with at least 1 dose of study drug) population, excluding data after discontinuation of study drug (last dose date + 7 days). From the overall cohort, any participant who had a history of CVD at baseline will be excluded from the CVD risk prediction since the ACC/AHA predicts primary (i.e., incident) risk of CVD (please see section 9.6 for sensitivity analysis about this). No participants had T2D at baseline as it was an exclusion criterion in the SURMOUNT-1 trial, so no participants will be excluded from the overall cohort for the T2D analysis. Table 1 provides the mapping of the risk-engine population characteristics with the SURMOUNT-1 patient population.

Table 1. Mapping between risk engine patient populations and SURMOUNT-1 patients

Risk Engines	Predicted Outcome	Patient Population	SURMOUNT-1 PTS who do not meet criterion at Baseline
ACC 10-year CVD	ASCVD: coronary death or nonfatal myocardial infarction, or fatal or nonfatal stroke	All Criteria Met: N = 1339 (53%)	
		Age >= 40	N = 890 (35%)
		Age <= 79	N = 2 (0.1%)
		Free of CVD	78 (3%)
		White/African Amer	546 (22%)
		All criteria met: N = 1085 (43%)	
CMDS 10-year T2D	T2D	Age >= 45	1234 (49%)
		Free of T2D	0 (0%)
		White or Black	546 (22%)

7.3.2 Participant Groups

The participant groups are dictated by the SURMOUNT-1 trial randomization and include participants assigned to TZP (5, 10, and 15 mg) and placebo. TZP doses will be evaluated separately and pooled vs. placebo.

7.4 Time Periods

Figure 1 illustrates the study time periods. Risks will be evaluated at baseline, week 24, and week 72 using model input variables collected at those times. The timepoints were chosen because 72 weeks is the primary endpoint for the trial and 24 weeks is an interim visit when all necessary model inputs were collected.

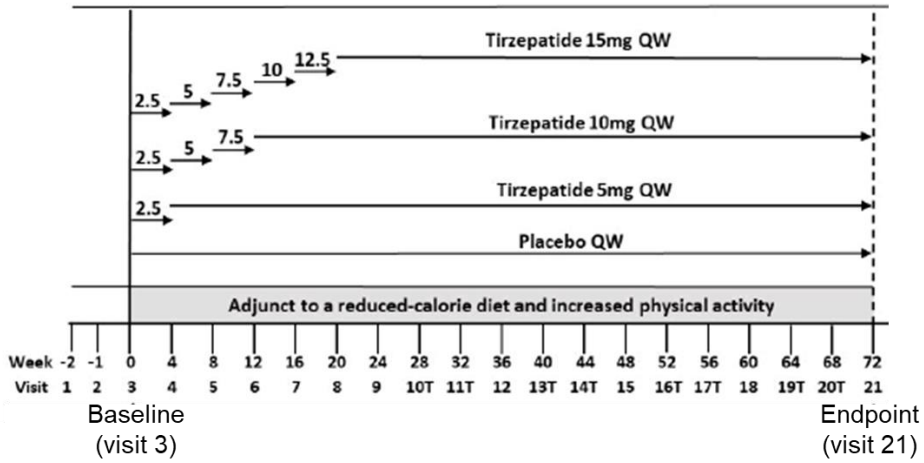

Figure 1. study time periods.

7.5 Variables/Measures

Table 2. presents the study variables and operational definitions. These represent the outcomes that are specified in the validated risk engines.[11-14]

Variables	Time Point	Trial Data Source	Definition/Derivation	Risk Engine	Collecting Schedule
Demographics and Health Factors					
Age	BL	ADSL.AGE	As reported	ACC/AHA; CMDS	Week 0
	Post-BL		Visit DT – BDT		
Sex	BL/Post-BL	ADSL.SEX	As reported	ACC/AHA; CMDS	Week 0
Race	BL/Post-BL	ADSL.RACE	As reported	ACC/AHA; CMDS	Week 0
Ethnicity	BL/Post-BL	ADSL.ETHNIC	As reported	ACC/AHA	Week 0
Smoking status (y/n)	BL/Post-BL	SU	sutrt = “TOBACCO” and SUOCCUR=”Y” and	ACC/AHA	Week 0

			SUENRTPT="ONGOING".		
Lab Values					
Total Cholesterol	BL/Post-BL	ADLBCN.AVAL	PARAMCD = "CHOLF50C"	ACC/AHA	Week 0, 12, 24, 36, 48, 60 and 72
HDL	BL/Post-BL	ADLBCN.AVAL	PARAMCD = "HDLF55C"	ACC/AHA; CMDS	Week 0, 24, and 72
Triglyceride	BL/Post-BL	ADLBCN.AVAL	PARAMCD = "TRIGF52C"	CMDS	Week 0, 12, 24, 36, 48, 60 and 72
Blood Glucose	BL/Post-BL	ADLBCN.AVAL	PARAMCD = "GLUCF30C"	CMDS	Week 0, 12, 24, 36, 48, 60 and 72
Vital Signs					
BMI	Baseline	ADSL.BMIBL	As reported	CMDS	Week 0, 4, 8, 12, 16, 20, 24, 36, 48, 60, 72
	Post-BL	ADVS.AVAL	PARAMCD = BMI		
SBP	BL	ADSL.SYSBPBL	As reported	ACC/AHA	Week 0, 4, 8, 12, 16, 20, 24, 36, 48, 60, 72
	Post-BL	ADVS.AVAL	PARAMCD = AVGSYSBP		
DBP		ADSL.DIABPBL	As reported	CMDS	Week 0, 4, 8, 12, 16, 20, 24, 36, 48, 60, 72
		ADVS.AVAL	PARAMCD = AVGDIABP		
Comorbidity					
Cardiovascular events	BL	ADSL.ASCVDFL	As reported	ACC/AHA	Week 0
	Post-BL	ADAJ.AVALC	*AVALC = myocardial infarction or hospitalization for unstable angina or hospitalization for heart failure or Coronary artery bypass graft (CABG) or Percutaneous coronary intervention (PCI) or stroke or Transient ischemic attack (TIA)	ACC/AHA	All visits

Medication Use					
Blood pressure lowering medication use (y/n)		ADCM.ACAT5 = “Antihypertensive” & ADCM.ANL06FL = “Baseline (Visit 3)		ACC/AHA	All visits

Note: Week 0 means baseline. ACC/AHA: American College of Cardiology/American Heart Association; BL: baseline; BDT: birthdate; BMI: body mass index; CMDS: Cardiometabolic Disease Staging; DBP: diastolic blood pressure; DT: date; HDL: high density lipoprotein; SBP: systolic blood pressure; AVALC will be evaluated when it is determined to be an EVENT to ensure we capture CEC adjudicated events only

8. Statistical Methods

8.1 Determination of Sample Size and/or Study Power

All ITT patients from SURMOUNT-1 trial will be used in this study including a total of 2539 patients with 643, 630, 636, and 630 patients in each of the Placebo, TZP 5mg, TZP 10mg and TZP 15mg treatment groups, respectively. Although the determination of sample size is not driven by statistical considerations, the sample size of 630 and 630 in the placebo and TZP highest dose (15mg) group will provide >= 99% power to detect a difference of 0.1 between the two treatment groups assuming a common standard deviation of 0.1 and a two-sided type I error rate of 0.05.

8.2 General Considerations

Analysis will be conducted using SAS Software, Version 9.4 or a more recent version.

Descriptive summary statistics will include:

- For categorical variables: number, number missing, frequency and percentage (with the percentage excluding the number missing in the denominator).
- For continuous variables: number, number missing, mean, median, standard deviation, standard error, minimum, maximum.

9. Analyses

9.1 Calculation of Risk Scores

The ACC/AHA and CMDS risk score calculations are based on a Cox regression model and a logistic regression, respectively. The model inputs will be used in a cross-sectional manner, such that the values for a given time period are not influenced or calculated relative to other time points. The details of the calculation of risk scores from each risk engine for each outcome are provided in appendix 1 (ACC/AHA) and appendix 2 (CMDS).

9.1 Adjustments for Bias and Confounding

The regression analysis will adjust for the baseline risk score or risk categories. The regression will also adjust for the stratification factor used in randomization in the SURMOUNT-1 trial including country and prediabetes status.

9.2 Evaluation of Quality of Balance Scores

No balance scores will be used for this study.

9.1 Missing Data

Missing predictors will not be imputed. Risk scores for patients with missing predictors will be missing. However, the risk scores will be modelled with MMRM that has built-in capabilities to handle missing data assuming missing is at random. Eight percent of the SURMOUNT-1 patients who discontinued study treatment before Week 24 will have their Week 24 and Week 72 risk scores missing.

9.1 Significance Levels and Multiplicity

Statistical significance tests will be conducted for risk score differences among treatment groups to facilitate interpretation of results. The 0.05 will be used as a guidance threshold for significance.

9.2 Primary Objective Analyses

The primary analysis will use the ACC/AHA risk engine[11-12] for CVD risk scores and the CDMS engine[13-14] for T2D risk scores. Risk scores will be calculated at baseline and Week 24 and Week 72 as well as the change of risk score from baseline.

A mixed model for repeated measures (MMRM) model will be performed on the change from baseline continuous scores with treatment group and baseline risk score as a covariate in the primary analysis. The least square mean, mean change from baseline, and difference of the risk scores will be reported. If the risk score distribution is skewed, then the risk scores will be analysed on log-scale.

The ACC/AHA CVD risk score will also be grouped into low (<5%), borderline (5 to <7.5%), intermediate (≥7.5 to <20%), or high (≥20%) risk categories, and the number and percentage of patients in each category will be reported overall and by treatment groups at each time point. Shift tables of the risk categories from baseline to post-baseline visit will also be provided.

The primary analysis will be performed among all patients without consideration for CVD events that occurred during the study. A sensitivity analysis will evaluate the robustness of this methodological choice (see section 9.6). Since no T2D events have been adjudicated with the available trial data, incident T2D will not be considered in the trial population for either risk engine.

9.3 Safety Analyses

The protocol-defined adverse events collected will be summarized by treatment arm according to section 8.2.

9.4 Subgroup Analyses

The primary analysis will also be conducted by key baseline characteristics including prediabetes status, BMI subgroups, and baseline CVD risk categories as determined by the ACC/AHA risk engine.

9.5 Interim Analyses

Not applicable.

9.6 Sensitivity Analyses

The following sensitivity analyses will be performed:

- The patients on TZP treatment will be merged into one group (TZP treated) and analysed versus the placebo group.
- Since the risk engines were developed and validated in narrower populations than the SURMOUNT-1 trial (see table 1), we will do the following sensitivity analyses:
    - For CVD, the primary analysis will be performed among patients with age >= 40 to <=79 years old at baseline.
    - For T2D, the primary analysis will be performed among White or Black patients with age >= 45.
    - For CVD, participants who experienced a CVD event between baseline and 24 weeks will be excluded from future CVD predictions (i.e., 24 and 72 week) and participants who experienced a CVD event prior to 72 weeks will be excluded from the 72-week prediction. This will be consistent with the ACC/AHA risk engine that predicts primary (i.e., incident) CVD events.

9.7 Interim Analysis

Not applicable.

10. Management and Reporting of Adverse Events/Adverse Reactions

10.1 Secondary Data Use

This is a non-interventional study based on secondary data use and therefore no ICSR reporting is required. The study protocol-defined AEs include: CVD events which are defined as: death due to CV cause, myocardial infarction, hospitalization for unstable angina, hospitalization for heart failure, coronary interventions (coronary artery bypass graft, percutaneous coronary intervention), and cerebrovascular events. All protocol-defined adverse events collected will be summarized in the final study report. No other AEs will be collected.

11. Protection of Human Participants

11.1 Participant Consent to Release Information

The original consent from the participants involved in the trial covers the planned analyses in this protocol.

11.2 Ethical Review and Regulatory Considerations

Observational studies will be submitted to ethical review boards (ERBs) for approval or waivers sought whenever required by local law. Regulatory authorities will be notified, and approval sought as required by local laws and regulations. Progress reports will be submitted to ERBs and regulatory authorities as required by local laws and regulations.

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Pharmacoepidemiology Practices (GPPs) and applicable laws and regulations of the country or countries where the study is being conducted, as appropriate.

12. Records Keeping, Data Reporting, Data Quality Assurance, and Publications

All information about this observational study and individual participant medical information resulting from this study are considered confidential, and disclosure to third parties is prohibited except for regulatory authorities and as applicable by law. Publications may result from this study.

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Appendix 1: ACC/AHA Risk Engine Calculation

Table 3. Equation parameters of the Pooled Cohort Equations for the Estimation of 10-year Risk for Hard ASCVD and specific Examples for Each Race and Sex

Subgroup	Formula
Women White	lp = (-29.799)*log(AGE) + 4.884*(log(AGE))^2 + 13.540*log(TOTCHOL) + (-3.114)*log(AGE)*log(TOTCHOL) + (-13.578)*log(HDL) + 3.149*log(AGE)*log(HDL) + 2.019*log(SBP)*HYPMED + 0.000*log(AGE)*log(SBP)*HYPMED + 1.957*log(SBP)*(1-HYPMED) + 0.000*log(AGE)*log(SBP)*(1-HYPMED) + 7.574*CURSMOK + (-1.665)*log(AGE)*CURSMOK + 0.661*T2D risk = 1 - 0.9665^(exp(lp - (-29.18)))
Women Black	lp = 17.114*log(AGE) + 0.000*(log(AGE))^2 + 0.940*log(TOTCHOL) + 0.000*log(AGE)*log(TOTCHOL) + (-18.920)*log(HDL) + 4.475*log(AGE)*log(HDL) + 29.291*log(SBP)*HYPMED + (-6.432)*log(AGE)*log(SBP)*HYPMED + 27.820*log(SBP)*(1-HYPMED) + (-6.087)*log(AGE)*log(SBP)*(1-HYPMED) + 0.691*CURSMOK + 0.000*log(AGE)*CURSMOK + 0.874*T2D, risk = 1 - 0.9533^(exp(lp - (86.61)))
Men White	lp = (12.344)*log(AGE) + 11.853*log(TOTCHOL) + (-2.664)*log(AGE)*log(TOTCHOL) + (-7.990)*log(HDL) + 1.769*log(AGE)*log(HDL) + 1.797*log(SBP)*HYPMED + 1.764*log(SBP)*(1-HYPMED) + 7.837*CURSMOK + (-1.795)*log(AGE)*CURSMOK + 0.658*T2D, risk = 1 - 0.9144^(exp(lp - (61.18)))
Men Black	lp = (2.469)*log(AGE) + 0.302*log(TOTCHOL) + 0.000*log(AGE)*log(TOTCHOL) + (-0.307)*log(HDL) + 0.000*log(AGE)*log(HDL) + 1.916*log(SBP)*HYPMED + 1.809*log(SBP)*(1-HYPMED) + 0.549*CURSMOK + 0.000*log(AGE)*CURSMOK + 0.645*T2D, risk = 1 - 0.8954^(exp(lp - (19.54)))

ASCVD = atherosclerotic cardiovascular disease, defined as first occurrence of nonfatal MI or CHD death, or fatal or nonfatal stroke.

AGE is in years; SBP = systolic blood pressure (mmHg); TOTCHOL = total cholesterol (mg/dL); HDL = high-density lipoprotein cholesterol (mg/dL); HYPMED = on hypertension medication (yes=1, no=0); CURSMOK = current smoker (yes=1, no=0); T2D = diabetes (yes=1, no=0).

Appendix 2: CMDS Risk Engine Calculation Algorithm

CMDS has two formulas for calculating subject risk score. One uses waist circumference (WC), and the other uses BMI. The one using WC is preferred over the one using BMI when WC is available. For this study, the formula using WC will be used to calculate the CDMS score.

CMDS score will be calculated for all SURMOUNT-1 patients. Patients who are Black will be coded 0, and patients who are non-Black (White or any other race category) will be coded 1.

Using BMI

The fitted main-effect logistic regression using REGARDS can be expressed as the following formula:

$$\begin{aligned}\Pr(\text{diabetes}) = \text{logit}^{-1}\,(&-8.464 - 0.014*\text{Age} + 0.053*\text{BMI} + 0.006*\text{SBP} \\ &+ 0.003*\text{DBP} + 0.062*\text{BG} - 0.018*\text{HDL} + 0.001*\text{TG} \\ &- 0.084*\text{Sex} - 0.446*\text{Race})\end{aligned}$$

Using Waist circumference (WC)

The fitted main-effect logistic regression using REGARDS can be expressed as the following formula:

$$\begin{aligned}\Pr(\text{diabetes}) = \text{logit}^{-1}\,(&-8.946 - 0.017*\text{Age} + 0.026*\text{WC} + 0.005*\text{SBP} \\ &+ 0.003*\text{DBP} + 0.061*\text{BG} - 0.017*\text{HDL} + 0.001*\text{TG} \\ &- 0.336*\text{Sex} - 0.499*\text{Race})\end{aligned}$$

The numbers in these formulas are the estimated intercept and coefficients. The right side presents the probability of incident diabetes for any individual; the function, $\text{logit}^{-1}(x)$, equals $\exp(x) / [1 + \exp(x)]$; Age, BMI (kg/m^2), SBP (mmHg), DBP (mmHg), BG (mg/dL), HDL (mg/dL), TG (mg/dL), and WC (cm) are the values of age, BMI, systolic blood pressure, diastolic blood pressure, blood glucose, HDL-c, triglycerides, and waist circumference (cm) respectively, for the individual; Sex equals 1 for male and 0 for female, and Race equals 1 for white and 0 for black. Thus, we can calculate the predictive risk probabilities for any patients using their personal values.