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Modelling Long-term Outcomes of Tirzepatide Compared to Lifestyle Management and other Anti-Obesity Medications as Treatment for Overweight and Obesity

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INTRODUCTION

BACKGROUND

- Obesity is an increasingly prevalent disease that is known to reduce quality of life, increase the risk of mortality, and cause numerous complications.
- Tirzepatide is a novel potential anti-obesity medication (AOM) under investigation in SURMOUNT-1[1] : a 72-week multi-center, Phase III trial which showed that patients receiving tirzepatide 15mg achieved 22.5% reduction in body weight and improvement in cardiometabolic measures.
- The long-term outcomes of treatment with AOMs, including tirzepatide 15mg, are unknown.

OBJECTIVE

- To estimate long-term clinical outcomes with tirzepatide 15mg vs semaglutide, phentermine / topiramate (P / T), naltrexone / bupropion (N / B), and lifestyle modification (LSM).

STUDY DESIGN

- A patient level simulation (PLS) that considers patient heterogeneity and event history was implemented using the discretely-integrated condition event (DICE) framework.
- Key outcomes were total life years (LYs) and quality-adjusted life years (QALYs) for each treatment option, as well as mean time to onset and percentage of patients experiencing key obesity-related complications. Selection of obesity-related complications was informed by a targeted literature review of published obesity cost-effectiveness analyses.

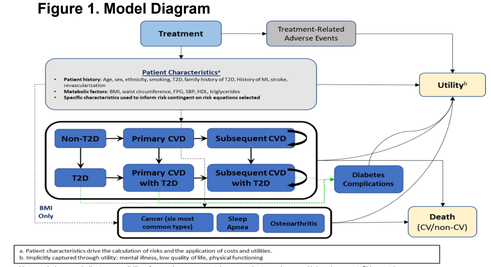
Modelled Population

- Modelled patient profiles (n=1,368) were based on data available from NHANES (2017 – March 2020). Following the inclusion criteria of the SURMOUNT-1 trial, included patients had either (1) a body mass index (BMI) ≥ 30 or (2) a BMI ≥ 27 and one obesity-related complication. Patients with type 2 diabetes (T2D) were excluded from the simulated cohort[1].
- Simulated patients were 47% male, had a mean age of 45.6 years at baseline, and mean BMI of 35.08 kg/m^2.

MODEL STRUCTURE

- A de novo model was developed to estimate the long-term outcomes for patients with obesity, based on short-term changes in BMI and other metabolic factors (i.e., high-density lipoprotein (HDL) cholesterol, systolic blood pressure (SBP), and fasting plasma glucose).
- Captured complications include T2D onset, primary and secondary CV events (MI, stroke, CV death, HF), diabetes complications (foot ulcers, amputation, blindness, renal disease), cancer (breast, colon, endometrial, kidney, esophageal, pancreatic), osteoarthritis, sleep apnea, and non-CV death.

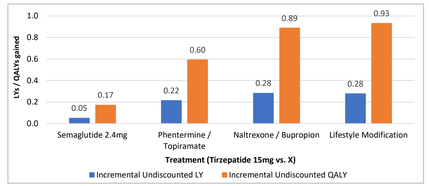
Figure 1. Model Diagram



KEY RESULT

- Base case results with 1,000 iterations projected that tirzepatide would deliver most LYs and QALYs among modelled comparators over a lifetime time horizon.
- Versus all treatments, this was driven primarily by the increased magnitude of weight loss and improvement in other cardiometabolic factors observed with tirzepatide.
- Compared to N / B and P / T, this effect was enhanced by tirzepatide's lower rate of treatment discontinuation (13%, 19%, and 23% per year, for tirzepatide 15mg, N / B, and P / T respectively).

Figure 2. LYs and QALYs gained with Tirzepatide 15mg



CONCLUSIONS

- Long-term projections using SURMOUNT-1 trial data showed that patients with overweight and obesity without diabetes and treated with tirzepatide are likely to experience improved quality-of-life, as well as a decreased incidence of obesity-related complications.
- Scenario analyses showed that:
  - Choice of diabetes risk equation has low impact on estimated life expectancy.
  - Using a very short time horizon of five years, tirzepatide shows robust quality of life improvement versus comparator treatments, particularly N / B and LSM.
  - Greater gains in QALYs and LYs are observed among patients in higher BMI classes.

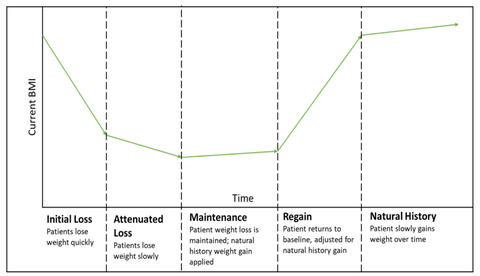
Model Inputs

- Changes in metabolic factors for each treatment were based on publicly available trial data, summarized in Table 1.
  - Based on observed patterns in weight loss trials (Table 1), patients on treatment moved through five different weight phases, initial loss, attenuated loss, maintenance, weight regain, and natural history (Figure 3).
  - During the natural history phase, the annual change in BMI and other metabolic factors was informed by data from a published systematic literature review.[2]
  - Change in metabolic parameters was placebo-adjusted for all treatments (i.e., the change for placebo from the trial efficacy estimand was subtracted from the published result, and the change for placebo from SURMOUNT-1 was added).

Table 1: Summary of Trials and Treatment in the Model

Treatment	Trial Data	Mean Weight Loss at End of Attenuated Loss Period
Tirzepatide 15mg	SURMOUNT-1[1]	22.50%
Semaglutide 2.4mg	STEP-1[3]	14.84%
Phentermine / Topiramate	EQUIP Study[4]	14.63%
Naltrexone / Bupropion	COR-II Study[5]	7.80%
Lifestyle Modification	Placebo arm of SURMOUNT-1[1]	2.40%

Figure 3. Diagram of BMI Trajectory Over Time



Results

Table 2: Summary of LY / QALY outcomes

Treatment	Total Undiscounted LY	Total Undiscounted QALY
Tirzepatide 15mg	35.89	24.35
Semaglutide 2.4mg	35.83	24.18
Phentermine / Topiramate	35.67	23.76
Naltrexone / Bupropion	35.60	23.46
Lifestyle Modification	35.60	23.42

- Tirzepatide 15mg was projected to delay the mean time to most complications. In all cases where the mean time to complication was shorter for tirzepatide 15mg, fewer patients experienced the complication.

Figure 4. Change in Mean Time to Event vs Tirzepatide 15mg

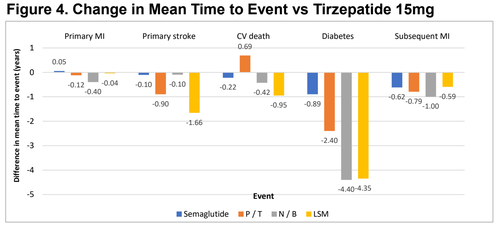
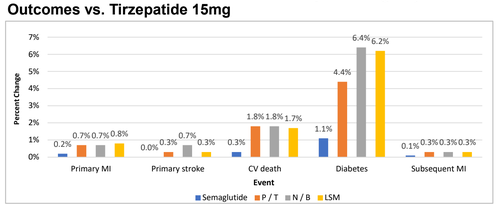


Figure 5. Increase in Number of Patients Experiencing Key Clinical Outcomes vs. Tirzepatide 15mg



Scenario Analyses

- Key scenario analyses were conducted to assess the impact of:
  - Different diabetes risk equations, developed using disparate populations; specifically, the Framingham Offspring study used in the base case was primarily conducted among White Americans; San Antonio and REGARDS equations included more Mexican Americans and Black Americans, respectively.
  - A shorter time horizon (five years)
  - Patients with more severe obesity at baseline (Class I or greater obesity and Class III or greater obesity).
- Scenario analyses showed that the use of alternative risk equations and shorter time horizon resulted in a pattern of LY benefit with tirzepatide 15 mg, consistent with that seen in the base case.
  - Patients with Class I+ or III+ obesity showed higher total LY than the base case analysis; in the former case, patients have less-severe disease; in the latter case, the patients with Class III+ obesity in the NHANES data were younger and more often female relative to the overall population.

Limitations

- It was a conservative assumption that all patients eventually rebound to baseline BMI after stopping treatment, and there is no risk reduction in complication onset due to weight loss for complications other than diabetes and CV events (only risk increase for weight gain).
- A key limitation of the analysis was that the risk equations to inform key predicted outcomes were not developed in a population identical to the SURMOUNT-1 trial.
  - Scenario analyses using the different diabetes risk equations demonstrated that the choice of risk equation had minor implications for the model results.

Abbreviations: AOM = anti-obesity medication; P / T = phentermine / topiramate; N / B = naltrexone / bupropion; LSM = lifestyle modification; PLS = patient-level simulation; DICE = discretely-integrated condition-event; BMI = body mass index; T2D = type 2 diabetes; CVD = cardiovascular disease; CV = cardiovascular; HF = heart failure; FPG = fasting plasma glucose; HDL = high-density lipoprotein; MI = myocardial infarction; SBP = systolic blood pressure; LY = life year; QALY = quality-adjusted life year

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