TREAT THE TRINITY

with

FOR PEOPLE WITH UNCONTROLLED TYPE 2 DIABETES

RYBELSUS®
semaglutide tablets

A GAME CHANGER. A LIFE CHANGER.

Early start for high CV risk T2D patients

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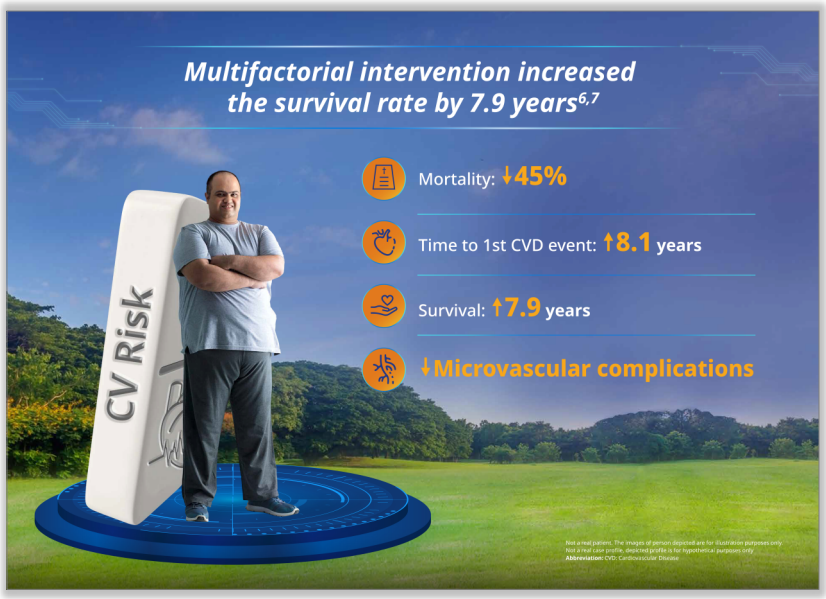
Problem Statement

- People with diabetes have 2-4 times increased CV risk.
- Excess weight in diabetes can increase the likelihood of developing a CV event by 33%.
- ~50% of deaths in people with T2D is attributed to CVD.
- 85% of deaths from CVD are due to atherosclerotic CVD (ASCVD), including myocardial infarction (MI) and stroke.
- ~1 in 5 of people with T2D experience their first CV event within first 5 years post diagnosis.
- Life expectancy is reduced by 12 years for a person with T2D (relatively younger i.e, less than 65 years of age) who has experienced a CV event.



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Cross talk between high glucose, weight and CV risk

- Excess weight reduces glucose uptake in the cells, increases insulin resistance, increases systemic inflammation, endothelial permeability, reduce cholesterol metabolism and promotes fat deposition leading to CVD.
- Each 1 kg reduction in body weight accounts for 0.1% HbA1c reduction
- DiRECT study has shown that ~50% achieved diabetes remission (sustained A1C<6.5 for 3 months without medications) in the weight management group vs control group.
- LOOK AHEAD trials showed >10% of weight loss in T2D had a 21% lower risk of CV death.
- STENO-2 trial had shown that multifactorial intervention (targeting glucose, weight and CV risk factors like BP, platelet aggregation and dyslipidemia) reduces mortality by 45%, reduces incidence of microvascular complications, increases survival by 7.9 years and delays the time to first CV event by 8 years.

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LOOK AHEAD

The Look AHEAD study was a multicenter, randomized clinical trial that examined the long-term effects of an intensive lifestyle intervention program designed to achieve and maintain weight loss by decreased caloric intake and increased physical activity. Eligible patients with type 2 diabetes and a body-mass index (BMI) of 25.0 or more were enrolled and randomly assigned either to participate in an intensive lifestyle intervention (intervention group) or to receive diabetes support and education (control group). An intensive lifestyle intervention focusing on weight loss reduced the risk of composite outcome of CV death, non-fatal acute MI, stroke, hospital admission for angina within 1 year in overweight or obese people with diabetes.

DiRECT

The Diabetes Remission Clinical Trial (DiRECT) was designed to determine whether a structured, intensive, weight management program, is a viable treatment for achieving durable normoglycaemia. Weight management intervention after 2 years resulted in mean weight loss of 7·6 kg, with 36% of participants in remission of type 2 diabetes. Of 36 in the intervention group who maintained over 10 kg weight loss at 2 years, 29 (81%) were in remission. It has shown that ~50% achieved diabetes remission (sustained A1C<6.5 for 3 months without medications) in the weight management group vs control group (guideline-based management).

STENO-2

Steno-2 Study, randomly assigned 160 patients with type 2 diabetes and persistent microalbuminuria to receive either intensive therapy or conventional therapy; the mean treatment period was 7.8 years. Patients were subsequently followed observationally for a mean of 5.5 years. The primary end point at 13.3 years of follow-up was the time to death from any cause. In at-risk patients with type 2 diabetes, intensive intervention with multiple drug combinations and behavior modification had sustained beneficial effects with respect to vascular complications and on rates of death from any cause and from cardiovascular causes.

Guideline recommendations for the use of glucose lowering agents with CV Safety/ Benefit

- Treating early with agents like GLP-1RA which has benefits on multiple organ systems is important to prevent chronic complications in T2D.
- People with diabetes initiated on GLP-1 RA within 1 to 2 years of T2D diagnosis had lower risk of CV events regardless of high baseline A1c.
- GLP-1 RAs were associated with significantly lower risks of MACE and all-cause mortality in patients with T2D at moderate cardiovascular risk.
- ADA 2024 has recommended GLP-1RAs as first-line therapy in T2D with high CV risk or ASCVD.
- ESC 2023 guidelines recommend GLP-1RA as preferred therapy to reduce CV risk in type 2 diabetes independent of glucose control and background anti-diabetic medications.

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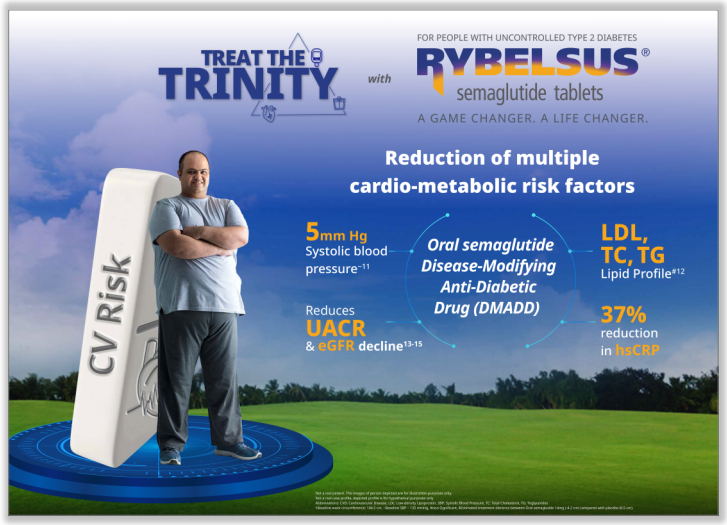
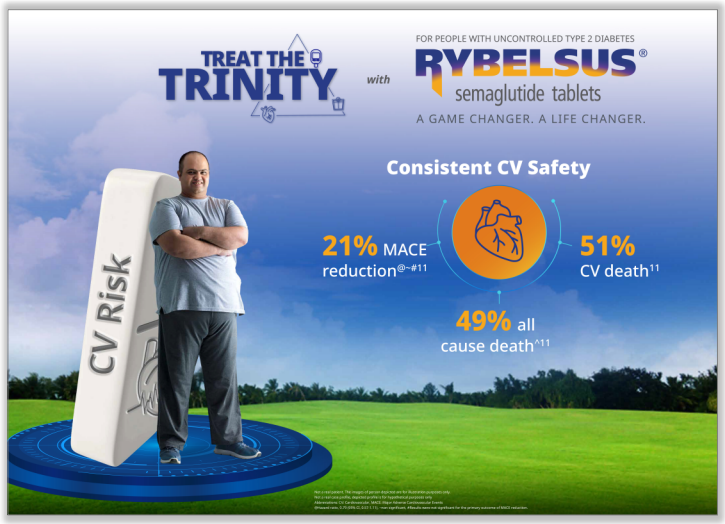
Addressing the "Trinity"

with oral semaglutide

- PIONEER trials have shown an HbA1c reduction of upto 1.5% (2.6% when baseline above 9%), weight reduction of upto 5kg and reduction of CV risk factors like BP upto 5 mm of Hg, hsCRP upto 37%, waist circumference upto 4.7 cms, total cholesterol, LDL and TGs.
- Real world (prospective and retrospective) studies on oral semaglutide has also shown significant reduction in body weight, HbA1c and CV risk factors.
- Oral semaglutide has an established safety profile in PwT2D with negligible risk of hypoglycaemia
- Oral Semaglutide has established CV Safety in T2D in PIONEER 6 trial with 21% non-significant MACE reduction, 51% CV death reduction and 49 % reduction in all cause death.
- In SUSTAIN 6 and PIONEER 6 combined, semaglutide showed consistent effects with 24% significant risk reduction in MACE versus comparators across varying CV risk.
- Data from the pooled analysis of oral and inj. Sema has shown that PwD on semaglutide can gain 1.7 more CVD free life-years
- The ongoing SOUL CVOT will provide further information about CV outcomes with oral semaglutide.





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SOUL

is a randomized, double-blind, parallel-group, placebo-controlled CV outcomes trial comparing oral semaglutide (14 mg once daily) with placebo, both in addition to standard of care, in individuals aged ⩾50 years with type 2 diabetes and evidence of ASCVD (coronary artery disease [CAD], cerebrovascular disease, symptomatic peripheral arterial disease [PAD]) and/or CKD (estimated glomerular filtration rate <60 mL/min/1.73 m2). The primary outcome is time from randomization to first occurrence of a major adverse CV event (MACE; a composite of CV death, nonfatal myocardial infarction or nonfatal stroke). This event-driven trial will continue until 1225 first adjudication-confirmed MACEs have occurred. Enrolment has been completed. Overall, 9650 participants were enrolled between June 17, 2019 and March 24, 2021 (men 71.1%, White ethnicity 68.9%, mean age 66.1 years, diabetes duration 15.4 years, body mass index 31.1 kg/m2, 8.0%). The most frequently used antihyperglycaemic medications at baseline were metformin (75.7%), insulin and insulin analogues (50.5%), sulphonylureas (29.1%), sodium-glucose cotransporter-2 inhibitors (26.7%) and dipeptidyl peptidase-4 inhibitors (23.0%). At randomization, 70.7% of participants had CAD, 42.3% had CKD, 21.1% had cerebrovascular disease and 15.7% had symptomatic PAD (categories not mutually exclusive). Prevalent heart failure was reported in 23.0% of participants. SOUL will provide evidence regarding the CV effects of oral semaglutide in individuals with type 2 diabetes and established ASCVD and/or CKD