Semaglutide oral 14 mg O.D. is not approved for treatment of ASCVD and/or chronic kidney disease. Safety and efficacy are not established for this use under clinical investigation

SOUL: Effects of oral semaglutide on cardiovascular outcomes in individuals with type 2 diabetes and established atherosclerotic cardiovascular disease and/or chronic kidney disease

BACKGROUND

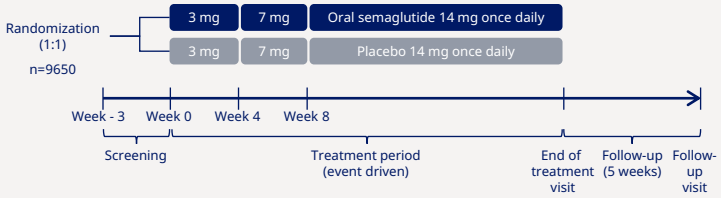
- CVD is a common cause of morbidity and mortality in individuals with T2D, with those individuals having a higher risk of CAD, HF, stroke, PAD and atrial fibrillation compared to those without T2D[1]
- Semaglutide is a GLP-1RA approved to improve glycemic control in individuals with T2D, available as a once-weekly injectable or as a once-daily oral tablet[2,3]
- Results from the SUSTAIN 6 trial demonstrated a significant 26% relative and a 2.3% absolute reduction in risk for the MACE composite endpoint in individuals with T2D with or at high ASCVD risk, with injectable semaglutide compared with placebo[4]
- Results from the PIONEER 6 trial demonstrated a 21% nonsignificant decrease in the incidence of MACE in individuals with T2D with high CVD risk, with oral semaglutide versus placebo and confirmed the noninferiority of oral semaglutide compared to placebo[5]
- Based on the results from the SUSTAIN 6 trial, and complemented by results from the PIONEER program , injectable (but not oral) semaglutide was granted a US FDA product label indication to reduce the risk for CV death, MI and stroke in individuals with T2D and established CVD[4,6]
- While PIONEER 6 successfully demonstrated CV safety, it was not powered to formally assess the CV efficacy of oral semaglutide and therefore the Semaglutide cardiovascular outcomes trial (SOUL) was designed[7]

STUDY DESIGN

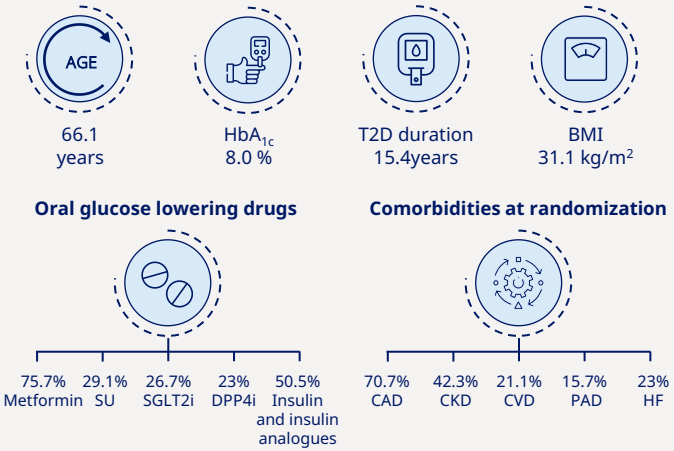
Randomized, double-blind, parallel-group, placebo-controlled

Adults ≥50 years, with T2D
- HbA_{1c} between 6.5%–10.0%

And at least one of the following conditions:
- CAD
- Cerebrovascular disease
- Symptomatic PAD
- CKD



BASELINE CHARACTERISTICS



ENDPOINTS

Primary outcome

- Time to first occurrence of MACE, a composite outcome consisting of:
  - CV death
  - Nonfatal MI
  - Nonfatal stroke

Confirmatory secondary outcome

- Time to first occurrence of a composite CKD outcome consisting of:
  - CV death
  - Kidney-related death
  - Persistent ≥50% reduction in eGFR (CKD-EPI)‡
  - Persistent eGFR (CKD-EPI) <15 ml/min/1.73 m2
  - Initiation of chronic kidney replacement therapy (dialysis or kidney transplantation)
- Time to occurrence of CV death
- Time to first occurrence of major adverse limb events, a composite outcome consisting of:
  - Acute limb ischemia hospitalization
  - Chronic limb ischemia hospitalization

SUMMARY

SOUL is a randomized, double-blind, placebo-controlled dedicated CVOT trial of oral semaglutide, the first oral GLP-1RA, in individuals with type 2 diabetes and established ASCVD and/or CKD. Data generated from this trial are expected to provide practicing clinicians with more information as to the optimal utilization of anti-hyperglycemic agents in type 2 diabetes, in an effort to reduce the risk of CV and kidney disease events.

ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CV, cardiovascular; CVD, cardiovascular disease; FDA, Food and Drug Administration; GLP-1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction; PAD, peripheral artery disease; T2D, type 2 diabetes.

1. Rawshani A et al. N Engl J Med. 2018;379:633-644; 2. Thethi TK, et al. Diabetes Obes Metab. 2020;22:1263-1277; 3. Aroda VR, et al. Diabetes Metab. 2019;45:409-418; 4. Marso SP, et al. N Engl J Med. 2016;375:1834-1844; 5.Husain M, et al. N Engl J Med. 2019;381:841-851; 6. Food and Drug Administration. Ozempic® Product Information. 2021; 7. McGuire DK et al. Diabetes Obes Metab. 2023 Jul;25(7):1932-1941.

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