Effects of semaglutide on functional capacity in patients with type 2 diabetes and peripheral arterial disease: rationale and design of the STRIDE trial

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Can once-weekly semaglutide improve walking distance in patients with PAD and T2D?

Background

- Peripheral arterial disease (PAD) is a manifestation of atherosclerotic disease characterised by obstruction in the arteries in the lower extremities.[1–4]
- The metabolic dysfunction seen in diabetes and obesity (including increased blood glucose, hypertension and dyslipidaemia) is closely associated with PAD;[4,5] ~30% of patients with PAD also have background type 2 diabetes (T2D) and these patients often have a poorer prognosis than those without diabetes.[2,3]
- Intermittent claudication (IC) is one of the first symptoms of PAD[6] and is associated with poor health-related quality of life (QoL).[7]
- Although anti-atherosclerotic drugs and lifestyle changes are recommended,[8] there are no effective drugs to specifically improve functional outcomes in PAD and T2D.[9,10]
- Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1RA) approved globally as an adjunct to diet and exercise for glycaemic control in patients with T2D,[11,12] and to reduce the risk of major adverse cardiovascular (CV) events (MACE) in those with T2D and CV disease in the USA.[11]
- In the T2D SUSTAIN clinical trial programme, once-weekly (OW) subcutaneous semaglutide 0.5 and 1.0 mg were superior for glycaemic control and weight loss vs placebo and a range of approved antidiabetes drugs.[13–21]
- In SUSTAIN 6, a dedicated CV outcomes trial, OW semaglutide resulted in a 26% reduction in three-point MACE vs placebo in patients with T2D at high CV risk.[22]
  - This reduction may be partly attributable to the anti-inflammatory and anti-atherosclerotic effects of semaglutide, which may also apply to PAD.[23]
- In addition to potential direct effects, semaglutide may have indirect effects in PAD;[24] for example, weight loss with semaglutide may impact patient functional capacity.

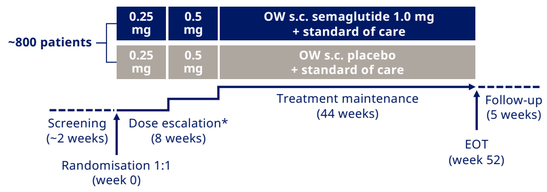
Purpose

- The STRIDE trial is intended to demonstrate the effect of OW semaglutide 1.0 mg vs placebo on walking ability in patients with T2D and PAD with IC.

Methods

- STRIDE (NCT04560998) is a 52-week, randomised, double-blind, placebo-controlled, phase 3b trial.
- Trial design is shown in **Figure 1** and eligibility criteria are shown in **Figure 2**.
- Approximately 800 patients will be randomised 1:1 to OW semaglutide 1.0 mg or placebo, both added to standard of care.
- The primary endpoint is change in maximum walking distance on a constant load treadmill test from baseline to week 52 (**Figure 3**).
- Secondary confirmatory endpoints are changes in pain-free walking distance and PAD-specific, health-related patient-reported outcomes (Vascular QoL Questionnaire-6) from baseline to week 52 (**Figure 3**).

Figure 1: Trial design



*Semaglutide dose escalated from a starting dose of 0.25 mg, doubled every 4 weeks until maintenance dose achieved. EOT, end of treatment; OW, once weekly; s.c., subcutaneous.

Figure 2: Inclusion and exclusion criteria

Inclusion criteria

- Male or female
- Age ≥18 years*
- T2D diagnosis ≥180 days prior to screening
- PAD with IC (Fontaine stage IIa for ≥90 days†)
- Pain-free WD ≥200 m on a flat treadmill test
- MWD ≤600 m on a constant load treadmill test
- ABI ≤0.9 or TBI ≤0.7

Exclusion criteria

- Conditions other than PAD that limit walking
- Planned surgery affecting walking ability
- Vascular revascularisation within 180 days prior to screening or planned arterial revascularisation
- Heart failure (NYHA class III–IV)
- MI, stroke, hospitalisation for unstable angina or TIA within 180 days prior to screening

*Age ≥20 years in Japan or Taiwan. †Based on patient interview. ABI, ankle-brachial index; IC, intermittent claudication; MI, myocardial infarction; MWD, maximum walking distance; NYHA, New York Heart Association; PAD, peripheral arterial disease; T2D, type 2 diabetes; TBI, toe-brachial index; TIA, transient ischaemic attack; WD, walking distance.

Figure 3: Trial objectives and endpoints

Objective

- To assess the effect of OW semaglutide 1.0 mg vs placebo on walking ability in patients with T2D and PAD with IC

Primary endpoint

- Change in maximum walking distance on a constant load treadmill test from baseline to week 52

Confirmatory secondary endpoints

- Change in pain-free walking distance from baseline to week 52
- Change in Vascular QoL Questionnaire-6 from baseline to week 52

Supportive secondary endpoints

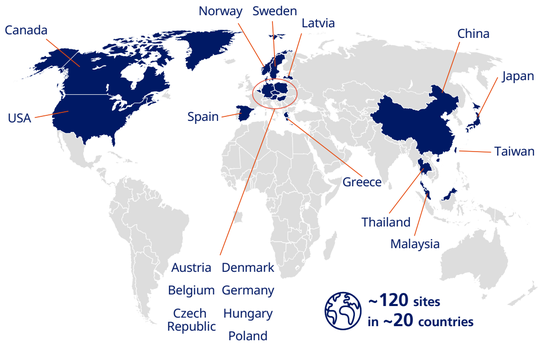
- Follow-up change in maximum walking distance on a constant load treadmill test at week 57 (Assessed after EOT)
- Follow-up change in pain-free walking distance on a constant load treadmill test at week 57 (Assessed after EOT)
- Change in HbA_{1c} from baseline to week 52
- Change in body weight from baseline to week 52
- Change in ABI and TBI from screening* to week 52
- Change in WIQ global score and SF-36 physical functioning domain from baseline to week 52
- Change in SBP from baseline to week 52
- Change in blood lipids from baseline to week 52

*Screening refers to week –2. ABI, ankle-brachial index; EOT, end of treatment; HbA_{1c}, glycated haemoglobin; IC, intermittent claudication; OW, once weekly; PAD, peripheral arterial disease; QoL, quality of life; T2D, type 2 diabetes; TBI, toe-brachial index; SBP, systolic blood pressure; SF-36, Short Form 36; WIQ, Walking Impairment Questionnaire.

Results

- The trial started in October 2020 and is currently recruiting.
- Enrolment is taking place at ~120 sites in ~20 countries across Asia, Europe, and North America (**Figure 4**).

Figure 4: STRIDE is a global trial



Conclusion

- STRIDE is the first and only dedicated trial with a GLP-1RA or other modern T2D drug that examines functional outcomes in PAD; it thus presents a unique trial design.
- Although major adverse limb events typically occur in the later stages of PAD, STRIDE will measure the effect of OW semaglutide on early functional outcomes that affect everyday living and QoL in patients with T2D, PAD and IC.
- STRIDE data will provide important clinical insights regarding the role of OW semaglutide in patients with T2D and PAD.

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