

# Profile of semaglutide in the management of type 2 diabetes: design, development, and place in therapy

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**Abstract:** Type 2 diabetes mellitus (T2DM) has become one of the leading causes of morbidity and mortality in developed countries. Low efficacy, weight gain, and hypoglycemia are the main pitfalls of previous treatments for T2DM. New therapies have been designed with the aim of improving the results in efficacy and quality of life. Glucagon-like peptide 1 (GLP-1) receptor agonists (GLP-1 RA) increase glucose-dependent insulin secretion, decrease gastric emptying, and reduce postprandial glucagon secretion. The last GLP-1 RA approved by the US Food and Drug Administration and European Medicines Agency was semaglutide. This review describes its pharmacology, core clinical data coming from the randomized controlled trials included in the development program, proven cardiovascular benefits, safety issues, and precautions for the use of semaglutide in special populations. Additionally, an overview of the positioning of semaglutide in T2DM therapy and practical issues regarding semaglutide initiation are offered.

**Keywords:** semaglutide, type 2 diabetes, pharmacological treatment, safety, clinical practice

## Introduction

Diabetes mellitus (DM) has become one of the leading causes of morbidity and mortality in developed countries.<sup>1</sup> It has also become one of the main sections of the health systems' budget.<sup>2</sup> The term DM includes, in fact, a long list of diverse diseases characterized by the presence of hyperglycemia. However, most cases can be diagnosed as type 1 (T1DM) and type 2 (T2DM) DM.<sup>3</sup> T2DM is a complex disease with a progressive course. Obesity, linked to insulin resistance, is the basis where relative insulin deficiency and other physiopathological alterations promote the development of metabolic and cardiovascular (CV) alterations.<sup>4</sup> It is also the most challenging problem to manage in clinical practice, significantly conditioning therapeutic adherence. Aggravating the above mentioned challenges, the classic treatments for T2DM (sulfonylurea [SU] and insulin) are associated with clinically relevant weight increases.<sup>5</sup>

Possibly, the second most significant barrier to achieve glycemic control objective in T2DM is the risk of hypoglycemia. Hypoglycemia events represent a tremendous cost burden in terms of quality of life, morbidity, and mortality.<sup>6-8</sup> Furthermore, SU and insulin are the most frequent causes of hypoglycemia.<sup>9</sup>

In recent years, new treatments have been developed with the aim of improving the results in efficacy and quality of life in people with T2DM.<sup>10</sup> Incretin agents, including dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists (GLP-1 RA), improve glucose control through several mechanisms,

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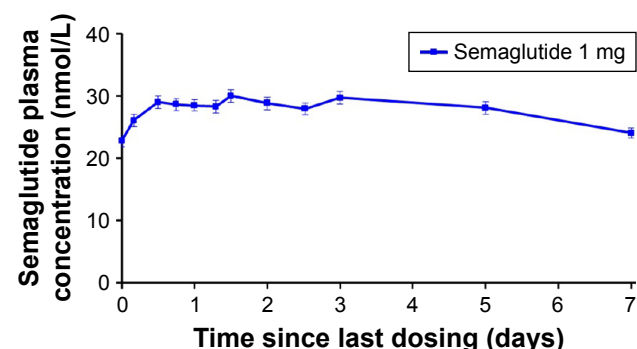
including the increase of glucose-dependent insulin secretion, decrease of gastric emptying, and reduction of postprandial glucagon secretion.<sup>11</sup>

The last GLP-1 RA approved by the US Food and Drug Administration and European Medicines Agency has been semaglutide.<sup>12</sup> This review describes its pharmacology, core clinical data coming from the randomized controlled trials (RCTs) included in the development program, proven CV benefits, safety issues, and precautions for the use of semaglutide in special populations. Additionally, an overview of the positioning of semaglutide in T2DM therapy and practical issues regarding semaglutide initiation are offered.

## Pharmacology and characteristics of the device

The efficacy and safety demonstrated by liraglutide were the basis for the development of semaglutide.<sup>13</sup> After testing several molecules, in search of increasing their half-life to achieve a more convenient dosage, semaglutide was chosen. The differences in the structure between liraglutide and semaglutide were the Ala to Aib substitution in position 8, a longer linker ( $\gamma$ Glu-2xOEG vs  $\gamma$ Glu), and an increase in the length of the fatty diacid chain from C16 to C18. It maintains 94% homology with human GLP-1. The affinity of semaglutide ( $0.38 \pm 0.06$  nM) toward the GLP-1 receptor was reduced by three times compared to liraglutide, while affinity with albumin was increased by 5.6 times.<sup>12</sup> This property confers a half-life of 165–184 hours<sup>14</sup> (~7 days) (Figure 1),<sup>15</sup> with a mean time for the maximum concentration (T<sub>max</sub>) of 24–36 hours.<sup>16</sup>

This long duration allows a weekly administration of semaglutide with doses that were established in preclinical



**Figure 1** Pharmacokinetic profile during a semaglutide 1 mg dosing interval at steady state in patients with T2D.

**Notes:** Reproduced from FDA Briefing Document. Endocrinologic and Metabolic Drugs Advisory Committee Meeting. October 18, 2017. Semaglutide s.c. OW NDA 209637. Available from: <https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm580460.pdf>. Accessed October 9, 2018.<sup>15</sup>

**Abbreviation:** T2D, type 2 diabetes mellitus.

studies in adults with T2DM.<sup>17</sup> The starting dose of once-weekly semaglutide is 0.25 mg. It should be increased to 0.5 mg after 4 weeks and can be further increased to 1 mg if required after at least 4 weeks.<sup>12</sup> As semaglutide is a prolonged-release GLP-1 RA, it can be administered without regard to meals. Likewise, it was verified that the presence of renal or hepatic insufficiency does not significantly alter the bioavailability of semaglutide.<sup>18,19</sup> The Jensen et al's study on people with hepatic impairment included an exploratory linear regression analysis to examine the influence of the serum albumin on overall semaglutide exposure, and the result does not show any significant correlation ( $R = -0.012$ ,  $P = 0.97$ ).<sup>19</sup>

Semaglutide is excreted in the urine (mainly, in which ~3% of the dose is excreted as intact semaglutide) and in the feces.<sup>20</sup>

Semaglutide requires selection of the dose in the injection device and removal/disposal of the needle after each injection. Semaglutide is available with three different pens for proper dosage (each box includes four of them for 1 month usage): 0.25 mg per once weekly injection, intended for initiation during the first 4 weeks; 0.5 mg weekly as first maintenance dose; and 1.0 mg weekly to be used under clinical judgment in patients without gastrointestinal symptoms after at least 4 weeks with the previous dose of 0.5 mg to further improve glycemic control.

## Clinical efficacy

### Efficacy and safety trials: SUSTAIN 1–7

The global program of clinical trial SUSTAIN (Semaglutide unabated Sustainability in Treatment of Type 2 Diabetes) included a series of Phase IIIA RCTs (SUSTAIN 1–5), designed to evaluate the efficacy and safety of semaglutide SC administered subcutaneously once a week in a range of people with T2DM, from those who have not received drugs to those who received oral antidiabetic drugs and/or insulin.<sup>21–25</sup>

Additionally, the SUSTAIN 7 trial compared semaglutide with dulaglutide. Both are long-acting GLP-1 RAs that are administered subcutaneously once weekly.<sup>26</sup>

Main characteristics of these RCTs are summarized in Table 1.

SUSTAIN 6 is a CV safety study and has been described separately.<sup>27</sup>

## Effects on glycemic control

The primary end point in the RCTs SUSTAIN 1–5 was the change in glycosylated hemoglobin (HbA<sub>1c</sub>) from baseline until the end of the treatment. In SUSTAIN 1–5, this was calculated using the estimated averages ( $\pm$  standard errors)

**Table 1** Trial design of the Phase 3 SUSTAIN 1–5 and 7 trials

SUSTAIN 1 (30 weeks)	SUSTAIN 2 (56 weeks)	SUSTAIN 3 (56 weeks)	SUSTAIN 4 (30 weeks)	SUSTAIN 5 (30 weeks)	SUSTAIN 7 (40 weeks)
<b>Trial design</b>					
Double-blinded, placebo-controlled, parallel-group, multicenter, multinational, four-armed trial	Double-blinded, double-dummy, active-controlled, parallel-group, multicenter, multinational, four-armed trial	Open-label, active-controlled, parallel-group, multicenter, multinational, two-armed trial	Open-label, active-controlled, parallel-group, multicenter, multinational, three-armed trial	Double-blinded, placebo-controlled, parallel-group, multicenter, multinational, four-armed trial	Open-label, active-controlled, parallel-group, multicenter, multinational, four-armed trial
<b>Background medication</b>					
None	MET with or without TZD	One to two oral antidiabetic drugs (OADs) of MET, TZD, or SU	MET and/or SU	Basal insulin with or without MET	MET
<b>Trial medication</b>					
Semaglutide 0.5 or 1.0 mg vs placebo (all sc once weekly)	Semaglutide 0.5 or 1.0 mg or placebo (sc once weekly) + sitagliptin 100 mg or placebo (oral once daily)	Semaglutide 1.0 mg vs exenatide ER 2.0 mg (both sc once weekly)	Semaglutide 0.5 mg or 1.0 mg (sc once weekly) vs insulin glargine (sc once daily, starting from 10 IU once daily)	Semaglutide 0.5 or 1.0 mg vs placebo (all sc once weekly)	Semaglutide 0.5 or 1.0 mg or dulaglutide 0.75 mg or 1.5 mg (both sc once weekly)
<b>Inclusion criteria</b>					
<ul style="list-style-type: none"> <li>T2DM <math>\geq 18</math> years on treatment with diet/exercise</li> <li>HbA<sub>1c</sub> 7.0%–10.0%</li> </ul>	<ul style="list-style-type: none"> <li>T2DM on treatment with MET or TZD or MET + TZD</li> <li>HbA<sub>1c</sub> 7.0%–10.5%</li> </ul>	<ul style="list-style-type: none"> <li>T2DM on treatment with 1–2 OADs (MET, TZD, MET + TZD, SU)</li> <li>HbA<sub>1c</sub> 7.0%–10.5%</li> </ul>	<ul style="list-style-type: none"> <li>T2DM insulin-naïve patients and on treatment with MET or MET + SU</li> <li>HbA<sub>1c</sub> 7.0%–10.0%</li> </ul>	<ul style="list-style-type: none"> <li>T2DM on treatment with basal insulin alone or in combination with MET</li> <li>HbA<sub>1c</sub> 7.0%–10.0%</li> </ul>	<ul style="list-style-type: none"> <li>T2DM on treatment with MET monotherapy</li> <li>HbA<sub>1c</sub> 7.0%–10.5%</li> </ul>
<b>Reference</b>					
Sorli et al <sup>21</sup>	Ahrén et al <sup>22</sup>	Ahmann et al <sup>23</sup>	Aroda et al <sup>24</sup>	Rodbard et al <sup>25</sup>	Pratley et al <sup>26</sup>

**Notes:** Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) 1–5+7 trials: NCT02054897, NCT01930188, NCT01885208, NCT02128932, NCT02305381, and NCT02648204. Sustain 7 column is shaded to differentiate that it is a Phase IIIb study (whilst the others are phase IIIa).

**Abbreviations:** ER, extended release; HbA<sub>1c</sub>, glycosylated hemoglobin; MET, metformin; sc, subcutaneous; SU, sulfonylurea; T2DM, type 2 diabetes; TZD, thiazolidinedione.

of a mixed model for repeated measurements analysis using data of “treatment without rescue treatment” of the subjects in the full analysis set. Semaglutide showed significant and sustained reductions in HbA<sub>1c</sub> vs comparator in all trials (Figure 2): –1.2% to –1.5% for the 0.5 mg dose and –1.5% to –1.8% with the 1 mg weekly dose.

In the SUSTAIN 7 trial, the HbA<sub>1c</sub> reductions were –1.5% and –1.8% with 0.5 and 1 mg dose of semaglutide, and –1.1% and –1.4% with 0.75 and 1.5 mg of dulaglutide, respectively.

## Weight reduction

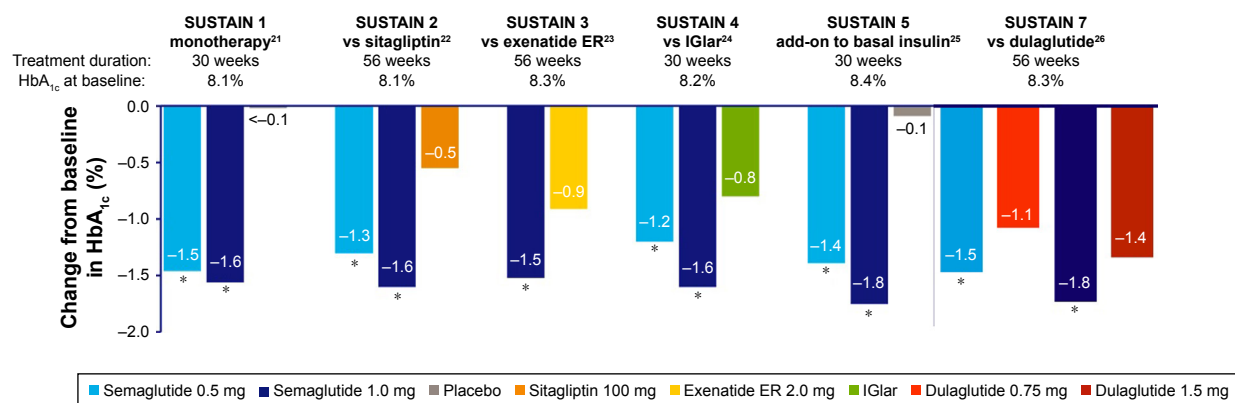
Obesity is a key factor in the etiology of the T2DM. Weight gain is associated with increased CV risk and a reduction in life expectancy.<sup>28,29</sup>

Semaglutide was associated with significant reductions in weight against the comparator across SUSTAIN 1–5 program: –3.5 to –4.3 kg for the 0.5 mg dose and –4.5

to –6.4 kg with the 1 mg weekly dose (Figure 3). In the case of semaglutide 1.0 mg, the weight loss was at least double that of the respective comparator in each trial.

The differences in weight reduction against each comparator were: –2.5 and –3.5 kg vs placebo, –1.4 and –4.2 kg vs sitagliptin, and –4.7 and –6.4 kg vs insulin glargine with 0.5 and 1 mg doses of semaglutide, respectively; only the dose of 1 mg weekly was tested against exenatide ER 2 mg weekly and the difference was –3.7 kg. In the SUSTAIN 7 trial, the weight reductions were –4.6, –6.5, –2.3, and –3 kg with the 0.5 mg, 1 mg dose of semaglutide and 0.75, 1.5 mg of dulaglutide, respectively.

Body composition changes induced by semaglutide were assessed by air displacement plethysmography after 12 weeks of treatment (weight loss 4–5 kg).<sup>30</sup> Three times greater loss of fat mass than lean body mass was observed. In a similar study by Blundell et al, appetite reduction was



**Figure 2** Change in HbA<sub>1c</sub> in SUSTAIN 1–5 and 7 RCTs.

**Note:** \* $P < 0.0001$  vs comparator.

**Abbreviations:** ER, extended release; HbA<sub>1c</sub>, glycosylated hemoglobin; IGLar, insulin glargine; RCTs, randomized controlled trials.

described as a possible mechanism of body weight loss, which led to lower daily energy intake (decrease of 24%), while there was no evidence that semaglutide increased the energy expenditure. Semaglutide also improved the perceived control of diet and a relatively lower preference for high-fat foods. When compared to placebo, there was no difference in the rate of nausea during meals as a possible cause for markedly reduced energy intake with semaglutide.

## Effects on blood pressure

The increase in blood pressure is a risk factor for CV morbidity and mortality in subjects with T2DM, and its reduction has shown clinical benefits for people with T2DM.<sup>31</sup>

Semaglutide was associated with sustained reductions in SBP from the beginning through the SUSTAIN program (Figure 4).<sup>21–26</sup>

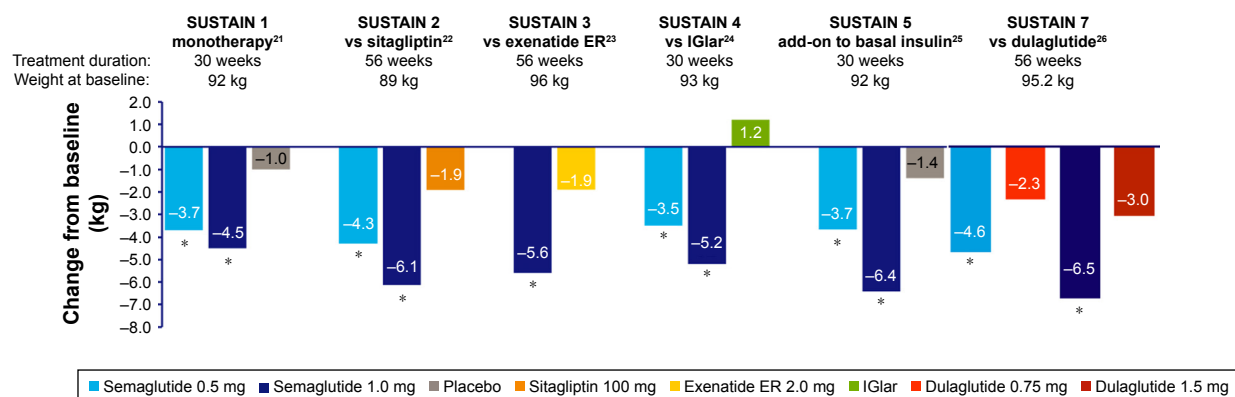
With the exception of SUSTAIN 1 trial,<sup>21</sup> which included subjects without prior treatment and with relatively short duration T2DM, and SUSTAIN 7 trial (comparing

dulaglutide), both dose levels of semaglutide were associated with significant reductions in SBP vs the comparator:  $-2.4$  to  $-5.1$  mmHg and  $-2.7$  to  $-7.3$  mmHg with the 0.5 mg and 1 mg weekly dose, respectively.

DBP was generally reduced with semaglutide. However, there were no significant differences when compared to the comparators.

## Cardiovascular and renal benefits: SUSTAIN 6 trial

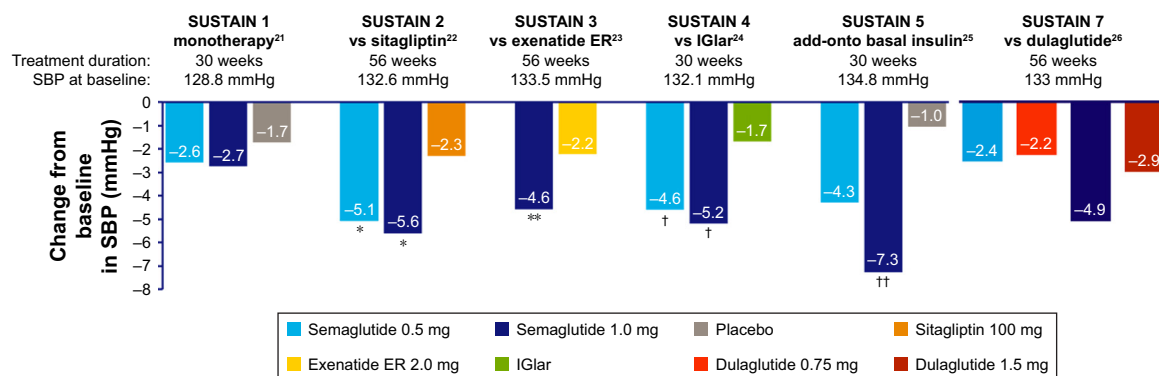
Based on recent ADA-EASD 2018 guidelines, addition of an agent with the evidence of CV risk reduction should be considered in patients with diabetes and established CV disease.<sup>32</sup> CV safety was studied in the SUSTAIN 6 study, a randomized, double-blind, placebo-controlled, four-armed, parallel-group trial of 109 weeks.<sup>27</sup> Additional glucose-lowering medication could be added to achieve glycemic control at the discretion of the investigators. Semaglutide reduced the risk of primary outcome by 26% vs placebo,



**Figure 3** Change in weight in SUSTAIN 1–5 and 7 RCTs.

**Note:** \* $P < 0.0001$  vs comparator.

**Abbreviations:** ER, extended release; IGLar, insulin glargine; RCTs, randomized controlled trials.



**Figure 4** Change in systolic blood pressure in SUSTAIN 1–5 and 7 RCTs.

**Notes:** \* $P < 0.005$  vs comparator; \*\* $P < 0.002$  vs comparator; † $P < 0.004$  vs comparator; †† $P < 0.001$ .

**Abbreviations:** ER, extended release; IGLar, insulin glargine; RCTs, randomized controlled trials.

nonfatal stroke by 39%, and nonfatal myocardial infarction by 26%. No difference in CV death was observed.

Additionally, the risk of new or worsening nephropathy (defined as persistent macroalbuminuria, a persistent doubling of the serum creatinine level and a creatinine clearance of  $<45$  mL/min/1.73 m<sup>2</sup>, or the need for continuous renal-replacement therapy) was significantly lower with semaglutide vs placebo (–36%). Differences in macroalbuminuria drove this effect.

Semaglutide resulted in reductions in HbA<sub>1c</sub> (–0.7% in the group receiving 0.5 mg and –1.0% in the group receiving 1.0 mg) and body weight (–2.9 kg in the group receiving 0.5 mg and –4.3 kg lower in the group receiving 1.0 mg) vs placebo, with similar rates of hypoglycemia between the groups.

## Indications

Semaglutide is indicated as monotherapy, when there is inadequate glycemic control with diet/exercise and when metformin is considered inappropriate due to intolerance or contraindications, and in combination with other glucose-lowering medication(s), including insulin, when these – together with diet and exercise – do not provide adequate glycemic control.<sup>12</sup>

## Administration in combination with oral antidiabetic drugs

Just as with other GLP-1 RAs, if semaglutide is administered in combination with a SU, a reduction in the dose of the SU should be considered, to reduce the risk of hypoglycemia.<sup>12</sup>

## Administration in combination with insulin

In general, when semaglutide is administered in combination with basal insulin, it is recommended that a reduction in the dose of basal insulin should be considered to reduce the

risk of hypoglycemia.<sup>12</sup> In the RCT SUSTAIN 5 (addition of semaglutide to basal insulin), the dose of insulin was reduced by 20% at randomization in patients with HbA<sub>1c</sub>  $<8\%$ .<sup>25</sup>

## Safety issues and precautions for the use of semaglutide in special populations

The more frequent adverse events associated with the use of GLP-1 RA were gastrointestinal reactions, such as nausea, vomiting, and diarrhea. They could be especially disturbing when treating patients with impaired renal function and dehydration. Nausea occurred in 17.0% and 19.9%, diarrhea in 12.2% and 13.3%, and vomiting in 6.4% and 8.4% of patients when treated with semaglutide 0.5 mg and 1 mg, respectively.<sup>12</sup> Most events were mild to moderate in severity and led to treatment discontinuation in 3.9% and 5% of patients, respectively.

Semaglutide should be discontinued if pancreatitis is suspected and caution should be exercised in patients with a history of pancreatitis.

As described with other GLP-1 RAs, pulse rate increased in all treatment groups, with higher increases for semaglutide vs comparators (1.7, 2.5 vs 0.4 bpm with semaglutide 0.5 mg, 1.0 mg vs comparator).<sup>33</sup> The real clinical significance of this finding is currently unknown.

Only in the SUSTAIN 6 study, the risk of retinopathy complications (vitreous hemorrhage, blindness, or conditions requiring treatment with an intravitreal agent or photocoagulation) was significantly higher vs placebo (HR, 1.76).<sup>27</sup> Rapid improvement in glucose control has been associated with a worsening of diabetic retinopathy.<sup>34</sup> A previous ophthalmological exam and specific follow-up (depending on individual metabolic and ophthalmologic situation) are advisable when semaglutide is initiated in patients treated with insulin and with a history of diabetic retinopathy or previous poor control (Table 2).<sup>15</sup>



**Table 2** Semaglutide as a helpful choice in challenging clinical scenarios<sup>a</sup>

Clinical scenario (ADA 2018) <sup>35</sup>	Concomitant treatment adjustment	Safe considerations	Observation (data for semaglutide 1 mg)
Diagnosis with HbA <sub>1c</sub> >9%	<ul style="list-style-type: none"> <li>If BP &lt;140/80 mmHg, review and decrease the antihypertensive treatment according to weekly monitoring</li> </ul>	<ul style="list-style-type: none"> <li>Information for reducing GI AEs<sup>b</sup></li> <li>BP monitoring</li> <li>Review and follow DRP<sup>15</sup></li> </ul>	Probably reach HbA <sub>1c</sub> target: >35% HbA <sub>1c</sub> <7% in 6 months <sup>21</sup>
Not at target on dual or triple oral therapy	<ul style="list-style-type: none"> <li>Withdraw DPP4i</li> <li>Withdraw or reduce SU</li> <li>Monitoring and adjusting antihypertensive treatment</li> </ul>	<ul style="list-style-type: none"> <li>Information for reducing GI AEs<sup>b</sup></li> <li>BP monitoring</li> <li>Review and follow DRP<sup>15</sup></li> </ul>	Mean HbA <sub>1c</sub> , weight, and SBP reduction (56 weeks): -1.5%, -5.6 kg, -4.6 mmHg <sup>23</sup> Probably reach HbA <sub>1c</sub> target: 67% HbA <sub>1c</sub> <7% (56 weeks) <sup>23</sup>
Patient with ASCVD not yet on an agent with evidence of CV risk reduction	<ul style="list-style-type: none"> <li>Withdraw DPP4i</li> <li>Withdraw or reduce SU</li> <li>HbA<sub>1c</sub> &lt;8% (69 mmol/mol), reduce daily insulin dose by 20%</li> </ul>	<ul style="list-style-type: none"> <li>Information for reducing GI AEs<sup>b</sup></li> <li>Monitoring SMBG to prevent hypoglycemia</li> <li>BP monitoring</li> <li>Review and follow DRP<sup>15</sup></li> </ul>	-16% RR reduction in CV death, nonfatal MI, or nonfatal stroke <sup>27</sup>
HbA <sub>1c</sub> not controlled under basal insulin	<ul style="list-style-type: none"> <li>HbA<sub>1c</sub> &lt;8% (69 mmol/mol), reduce daily insulin dose by 20%</li> <li>Withdraw DPP4i</li> <li>Withdraw or reduce SU</li> </ul>	<ul style="list-style-type: none"> <li>Information for reducing GI AEs<sup>b</sup></li> <li>Monitoring SMBG to prevent hypoglycemia</li> <li>BP monitoring</li> <li>Review and follow DRP<sup>15</sup></li> </ul>	Mean HbA <sub>1c</sub> , weight, and SBP reduction (30 weeks): -1.8% (20.2 mmol/mol), -6.4 kg, and -6.3 mmHg <sup>25</sup> Probably reach HbA <sub>1c</sub> target: 79% HbA <sub>1c</sub> <7% (30 weeks) <sup>25</sup> Mean insulin dose reduction: -15% <sup>25</sup>

**Notes:** <sup>a</sup>Definition of challenging clinical scenarios is as described in ADA 2018 antihyperglycemic therapy in type 2 diabetes recommendations.<sup>35</sup> <sup>b</sup>Information to patients about managing food intake and reducing fat content.<sup>37</sup> Consider semaglutide dose reduction.<sup>38</sup>

**Abbreviations:** CV, cardiovascular; DRP, diabetic retinopathy; GI, gastrointestinal; MI, myocardial infarction; SMBG, self-monitoring of blood glucose; AEs, adverse events; ADA, American Diabetes Association; HbA<sub>1c</sub>, glycosylated hemoglobin; DPP4i, dipeptidyl peptidase-4 inhibitors; ASCVD, atherosclerotic cardiovascular disease; RR, relative risk.

## Elderly population

Efficacy and safety of semaglutide across the SUSTAIN program (1–5 trials) in people younger and older than 65 years have been compared in a post hoc analysis. Similar reductions in HbA<sub>1c</sub> and mean body weight with semaglutide occurred in both age groups. The safety profile was also indistinguishable, except for a higher rate of premature treatment discontinuations caused by gastrointestinal adverse events in elderly vs non-elderly patients.<sup>33</sup> No dose adjustment was required based on age.

## Renal or hepatic impairment

No dose adjustment was required for patients with mild, moderate, or severe (estimated glomerular filtration rate ≥15 to <30 mL/min) renal or hepatic impairment.<sup>12</sup> Information with regard to the use of semaglutide in patients with severe hepatic impairment is limited.

## Conclusion and practical positioning of semaglutide in type 2 diabetes therapy

Practical considerations on possible clinical scenarios where semaglutide could be an interesting option in the treatment of T2DM are depicted in Table 2. These clinically challenging

situations are based on the crossroads described in the American Diabetes Association algorithm for pharmacological treatment of T2DM.<sup>35</sup> However, these situations and recommendations are similar to those found in other clinical guidelines for the treatment of T2DM.<sup>32,36</sup> Adjustment of concomitant treatment, safety cautions, and efficacy expectancy are also detailed.

The higher potency in reducing HbA<sub>1c</sub> compared to other GLP-1 RAs and oral agents makes semaglutide an advantageous choice for T2DM treatment, allowing to reach glycemic targets in a broad T2DM population. The clinically relevant reductions in weight and SBP along with proven CV benefits in the SUSTAIN 6 trial support its preferred use in persons with established CV disease.<sup>27,35</sup> Gastrointestinal tolerance is the main barrier for adherence to GLP-1 RA. Information to patients about managing food intake and reducing fat content may reduce the incidence of nausea and vomiting.<sup>37</sup> If gastrointestinal side effects are observed, dose titration should be considered, by maintaining or reducing the semaglutide dose to 0.5 or 0.25 mg.<sup>36</sup>

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## Author contributions

Both authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

## Disclosure

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