Efficacy and safety of once-weekly semaglutide low dose 0.5 mg vs once-weekly dulaglutide high dose 1.5 mg in type 2 diabetes: a *post hoc* analysis of SUSTAIN 7

Richard E. Pratley[1]; Vanita R. Aroda[2]; Thomas Hansen[3]; Ildiko Lingvay[4]; Jörg Lüdemann[5]; Trine Vang Skjøth[3]; Adie Viljoen[6]

[1]AdventHealth Orlando, Translational Research Institute for Metabolism and Diabetes, Orlando, FL, USA; [2]Brigham and Women's Hospital, Boston, MA, USA; [3]Novo Nordisk A/S, Søborg, Denmark; [4]University of Texas Southwestern Medical Center, Dallas, TX, USA; [5]diabetes-falkensee, Diabetes Centre and Centre for Clinical Studies, Falkensee, Germany; [6]Lister Hospital, Stevenage, UK.

(qrs.ly/e5abn8z)

Aim

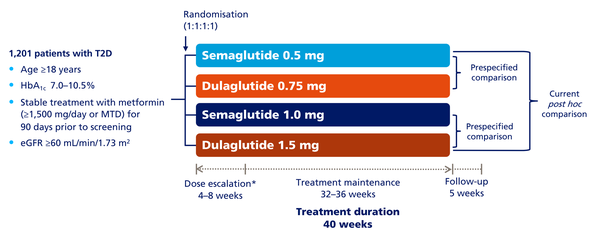
- Semaglutide (Novo Nordisk, Denmark) is a glucagon-like peptide-1 analogue indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes (T2D).[1]
- In SUSTAIN 7, an international, open-label, parallel-group trial, adults with inadequately controlled T2D were randomised (1:1:1:1) to receive subcutaneous semaglutide once weekly or dulaglutide once weekly at low (0.5 vs 0.75 mg, respectively) or high (1.0 vs 1.5 mg, respectively) doses.[2]
  - » Semaglutide provided superior glycaemic control and reductions in body weight vs dulaglutide at both low- and high-dose drug comparisons.[2]
- The aim of this *post hoc* analysis was to compare the effects of semaglutide low (0.5 mg) vs dulaglutide high (1.5 mg) dose at week 40.
  - » This comparison was **not prespecified** in the primary analysis of SUSTAIN 7.[2]
  - » This comparison was implemented to reflect options available in clinical practice and to ensure a thorough assessment of clinical efficacy and safety.

Methods

SUSTAIN 7 trial design (Figure 1)

- Data were collected from all patients randomised and exposed to treatment (full analysis set), and the data analysed in this *post hoc* analysis were prior to use of any rescue medication.

Figure 1: SUSTAIN 7 trial design[2]



*Semaglutide dose escalation from starting dose of 0.25 mg once weekly, dose doubled every 4 weeks until trial maintenance dose reached. Dulaglutide 0.75 mg and 1.5 mg dosed once weekly without dose escalation. eGFR, estimated glomerular filtration rate; MTD, maximum tolerated dose.

Results

Baseline characteristics and demographics

- Baseline characteristics were broadly consistent between semaglutide and dulaglutide (Table 1).
  - » Mean age was 56 years. Baseline HbA_{1c} was 8.2–8.3%; diabetes duration 7.6–7.7 years.

Table 1: Baseline characteristics and demographics

		Low-dose semaglutide 0.5 mg (n=301)	High-dose dulaglutide 1.5 mg (n=299)
Male, n (%)		169 (56.1)	171 (57.2)
Female, n (%)		132 (43.9)	128 (42.8)
Age, years		56 (10.9)	56 (10.6)
Diabetes duration, years		7.7 (5.9)	7.6 (5.6)
HbA_{1c}	%	8.3 (1.0)	8.2 (0.9)
	mmol/mol	67.5 (10.5)	66.1 (9.7)
FPG	mg/dL	176.3 (45.7)	172.5 (41.2)
	mmol/L	9.8 (2.5)	9.6 (2.3)
Body weight, kg		96.4 (24.4)	93.4 (21.8)
BMI, kg/m²		33.7 (7.1)	33.1 (6.6)
SBP, mmHg		134 (14.8)	132 (13.6)
DBP, mmHg		81 (9.0)	80 (8.7)

Values are mean (SD) unless otherwise indicated. BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; SBP, systolic blood pressure; SD, standard deviation.

Change in HbA_{1c} and body weight from baseline, and proportions of subjects achieving targets

- Low-dose semaglutide 0.5 mg resulted in similar improvements in glycaemic control and significantly greater weight loss vs high-dose dulaglutide 1.5 mg at week 40 (Figure 2).
- Similar proportions of subjects achieved HbA_{1c} <7.0% and ≤6.5%, but with low-dose semaglutide 0.5 mg, significantly larger proportions of subjects achieved weight loss ≥5% and ≥10% compared with high-dose dulaglutide 1.5 mg (Figure 3).

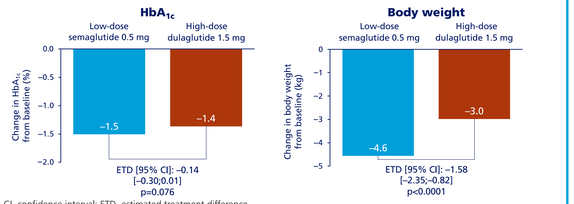
Change in systolic and diastolic blood pressure from baseline

- There were no significant differences in change from baseline in systolic and diastolic blood pressure between low-dose semaglutide 0.5 mg and high-dose dulaglutide 1.5 mg (Table 2).

Safety

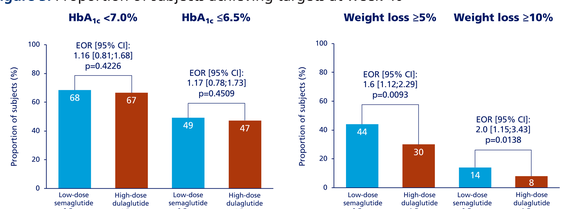
- The rate of adverse events (AEs) and serious AEs overall was similar for low-dose semaglutide 0.5 mg and high-dose dulaglutide 1.5 mg (Table 3).
- The rate of gastrointestinal (GI) AEs was similiar for low-dose semaglutide 0.5 mg and high-dose dulaglutide 1.5 mg; the GI AEs were mainly mild or moderate for both treatment groups (Table 3).
- The proportions of subjects discontinuing treatment due to any AE or due to GI AEs were similar for low-dose semaglutide 0.5 mg and high-dose dulaglutide 1.5 mg (Table 3).

Figure 2: Change in HbA_{1c} and body weight from baseline at week 40 — **Key result**



CI, confidence interval; ETD, estimated treatment difference.

Figure 3: Proportion of subjects achieving targets at week 40



CI, confidence interval; EOR, estimated odds ratio.

Table 2: Change in systolic and diastolic blood pressure from baseline at week 40

		Low-dose semaglutide 0.5 mg	High-dose dulaglutide 1.5 mg
SBP	Baseline, mmHg	134 (14.8)	132 (13.6)
	Change from baseline at week 40, mmHg	−2.4 (0.8)	−2.9 (0.8)
	ETD [95% CI]	0.42 [−1.68;2.52]	
	p-value	0.697	
DBP	Baseline, mmHg	81 (9.0)	80 (8.7)
	Change from baseline at week 40, mmHg	−0.6 (0.5)	−0.0 (0.5)
	ETD [95% CI]	0.54 [−1.86;0.79]	
	p-value	0.426	

Values are mean (SD) unless otherwise indicated. CI, confidence interval; DBP, diastolic blood pressure; ETD, estimated treatment difference; SBP, systolic blood pressure; SD, standard deviation.

Table 3: Adverse events by treatment

	Low-dose semaglutide 0.5 mg				High-dose dulaglutide 1.5 mg			
	n	%	E	R	n	%	E	R
All AEs	**204**	**68**	**966**	**412.7**	**221**	**74**	**957**	**402.6**
Serious AEs	**17**	**6**	**23**	**9.8**	**22**	**7**	**33**	**13.9**
Fatal events *†	**1**	**<1**	**1**	**0.4**	**2**	**1**	**5**	**2.0**
AEs leading to premature treatment discontinuation	**24**	**8**	**46**	**19.7**	**20**	**7**	**51**	**21.5**
GI AEs leading to premature treatment discontinuation	16	5	27	11.5	14	5	37	15.6
GI AEs	**129**	**43**	**394**	**168.3**	**143**	**48**	**393**	**165.4**
Mild	108	36	317	135.4	125	42	300	126.2
Moderate	40	13	57	24.4	39	13	80	33.7
Severe	9	3	20	8.5	8	3	13	5.5
Most frequent GI AEs								
Nausea	68	23	145	62.0	60	20	108	45.4
Diarrhoea	43	14	79	33.8	53	18	75	31.6
Vomiting	31	10	51	21.8	29	10	40	16.8

AEs include events that had an onset, or increase in severity, from first exposure to the planned follow-up visit scheduled 5 weeks (+7-day visit window) after the end of treatment visit at week 40 (on-treatment data). *AEs include events that had an onset, or increase in severity, from randomisation to the end of trial regardless of treatment or rescue medication status (in-trial data). †One subject receiving dulaglutide 1.5 mg had four events resulting in a fatal outcome. AE, adverse event; E, events; GI, gastrointestinal; R, rate of events per 100 patient-years.

Discussion

- In the original SUSTAIN 7 study, semaglutide was superior to dulaglutide at both low- and high-dose drug comparisons in improving glycaemic control and reducing body weight, and had a similar safety profile, in subjects with T2D.
- In this *post hoc* analysis of the SUSTAIN 7 trial, the comparison of low-dose semaglutide 0.5 mg vs high-dose dulaglutide 1.5 mg showed a similar glycaemic control, but with more weight loss and more subjects achieving ≥5% and ≥10% weight loss with low-dose semaglutide 0.5 mg vs high-dose dulaglutide 1.5 mg after 40 weeks, with a similar safety profile in subjects with T2D.
- These results suggest that the low dose of semaglutide 0.5 mg can provide greater weight-loss benefit to patients with T2D vs high-dose dulaglutide 1.5 mg, alongside similar glycaemic control and a similar safety profile.

Conclusion

- Subcutaneous low-dose semaglutide 0.5 mg once weekly showed greater weight loss and similar improvements in glycaemic control vs subcutaneous high-dose dulaglutide 1.5 mg once weekly at week 40, and with a similar safety profile in subjects with T2D, previously uncontrolled on metformin treatment.

This study was sponsored by Novo Nordisk and is registered with ClinicalTrials.gov (NCT02648204).
Presenter Richard Pratley has received consulting fees from AstraZeneca, GlaxoSmithKline, Glytec LLC, Janssen, Ligand Pharmaceuticals, Lilly, Merck, Mundipharma, Novo Nordisk, Pfizer, and Sanofi; has received grants from Lexicon Pharmaceuticals, Ligand Pharmaceuticals, Lilly, Merck, Novo Nordisk, and Sanofi; and lecture and other fees from AstraZeneca and Novo Nordisk. All honoraria and fees were directed to AdventHealth, a non-profit organisation.
The authors are grateful to Emre Yildirim, Novo Nordisk, for review of and input to the poster, and to Heather Mittman, AXON Communications (supported by Novo Nordisk), for writing assistance.
Presented at the 55th Annual Meeting of the European Association for the Study of Diabetes, 16–20 September 2019, Barcelona, Spain.

References: (**1**) Novo Nordisk. Ozempic® (semaglutide) Prescribing Information 2019. Available at: https://www.novo-pi.com/ozempic.pdf. Accessed August 2019; (**2**) Pratley RE et al. Lancet Diabetes Endocrinol 2018;6:275–86.