Survodutide, a glucagon receptor/glucagon-like peptide-1 receptor (GCGR/GLP-1R) dual agonist, improves metabolic risk factors in adults living with obesity: Analysis of a placebo-controlled, randomized phase 2 trial

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Objective

- To further analyze the phase 2 trial of survodutide in people living with obesity (NCT04667377), to explore:
  - Changes in waist circumference and FPG according to baseline HbA1c level (post hoc)
  - Changes in disease stage according to the EOSS and the CMDS system (pre-specified)

Conclusion

- In this post hoc analysis of people with obesity, treatment with the GCGR/GLP-1R dual agonist survodutide was associated with clinically meaningful reductions in waist circumference and FPG in those with normoglycemia or pre-diabetes, as well as improvements in stage of obesity

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Introduction

- Combining GCGR agonism with GLP-1R agonism may enhance body weight reduction by increasing energy expenditure as well as decreasing food intake[1]
- Survodutide (BI 456906) is a GCGR/GLP-1R dual agonist under investigation for chronic weight management in people living with obesity[2]
- In a multinational phase 2 trial, survodutide elicited up to 18.7% mean reduction in body weight after 46 weeks of treatment (according to actual maintenance doses) in people living with obesity without diabetes[3]

Methods

- In this post hoc analysis of a double-blind trial, 387 people aged ≥18 to <75 years with BMI ≥27 kg/m² without diabetes were randomized 1:1:1:1:1 to once-weekly subcutaneous placebo or survodutide 0.6, 2.4, 3.6, or 4.8 mg for 46 weeks: 20 weeks of dose escalation (when dose could also be adjusted for GI tolerability) then 26 weeks maintenance
- Evaluations included changes in waist circumference and FPG according to baseline HbA1c levels (post hoc), and changes in disease stage according to the EOSS and the CMDS system (pre-specified)
- Data were analyzed descriptively for all participants receiving ≥1 dose of study drug with data for ≥1 efficacy endpoint, i.e. the FAS, according to doses received during the maintenance period (i.e. actual treatment) and those assigned at randomization (i.e. planned doses) using on-treatment data

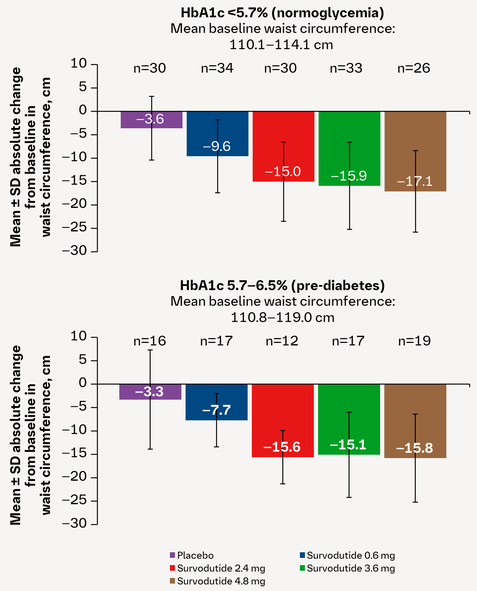
Results

- Baseline characteristics were similar across dose groups

Waist circumference and FPG

- At Week 46, survodutide reduced waist circumference up to 17.1 cm by actual treatment – of similar magnitude across baseline HbA1c levels (**Figure 1**)

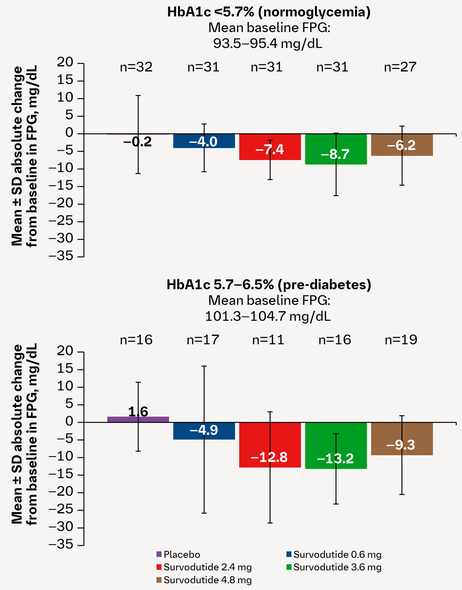
Figure 1. Waist circumference at Week 46



Data are mean ± SD for the FAS according to actual maintenance doses

- At Week 46, survodutide reduced FPG up to 13.2 mg/dL (0.73 mmol/L) by actual treatment – larger reductions were observed in participants with HbA1c 5.7–6.5% vs <5.7% (**Figure 2**)
- Reductions in waist circumference and FPG were similar when treatment groups were analyzed by planned doses

Figure 2. FPG at Week 46



Data are mean ± SD for the FAS according to actual maintenance doses

Disease staging

- Survodutide was associated with improvement in obesity stage by EOSS and CMDS at Week 46
- In all dose groups, more survodutide recipients improved EOSS than worsened (**Table 1**)
- Overall, 25.3% of survodutide recipients improved vs 8.2% of placebo recipients
- Only 7.1% of survodutide recipients worsened vs 10.2% of placebo recipients

Table 1. Edmonton Obesity Staging System[4] at Week 46

No change | Improved | Worsened

	Baseline EOSS				Week 46	
Week 46 EOSS	**0**	**1**	**2**	**3**	**Worsened**	**Improved**
Placebo					5/49 (10.2%)	4/49 (8.2%)
0	15	2	0	0		
1	2	13	2	0		
2	0	2	12	0		
3	0	1	0	0		
Survodutide 0.6 mg					4/48 (8.3%)	10/48 (20.8%)
0	10	3	2	1		
1	2	12	3	0		
2	1	1	11	1		
3	0	0	0	1		
Survodutide 2.4 mg					2/49 (4.1%)	10/49 (20.4%)
0	12	6	3	0		
1	1	11	1	0		
2	1	0	12	0		
3	0	0	0	1		
Survodutide 3.6 mg					2/50 (4.0%)	13/50 (26.0%)
0	7	7	2	0		
1	0	12	4	0		
2	1	1	13	0		
3	0	0	0	1		
Survodutide 4.8 mg					6/51 (11.8%)	17/51 (33.3%)
0	11	12	2	0		
1	1	8	3	0		
2	1	4	8	0		
3	0	0	0	0		

Data are for the FAS according to planned maintenance doses

- In all dose groups, more survodutide recipients improved CMDS than worsened (**Table 2**)
- Overall, 27.3% of survodutide recipients improved vs 4.1% of placebo recipients
- Only 8.6% of survodutide recipients worsened vs 10.2% of placebo recipients

Table 2. Cardiometabolic Disease Staging system[5] at Week 46

No change | Improved | Worsened

	Baseline CMDS					Week 46	
Week 46 CMDS	**0**	**1**	**2**	**3**	**4**	**Worsened**	**Improved**
Placebo						5/49 (10.2%)	2/49 (4.1%)
0	15	1	0	0	0		
1	2	24	1	0	0		
2	0	2	3	0	0		
3	0	0	0	0	0		
4	0	0	0	1	0		
Survodutide 0.6 mg						3/48 (6.3%)	12/48 (25.0%)
0	10	4	2	0	1		
1	1	16	2	2	0		
2	0	1	4	1	0		
3	1	0	0	2	0		
4	0	0	0	0	1		
Survodutide 2.4 mg						5/49 (10.2%)	15/49 (30.6%)
0	13	11	0	0	0		
1	3	14	3	1	0		
2	0	2	1	0	0		
3	0	0	0	0	0		
4	0	0	0	0	0		
Survodutide 3.6 mg						2/50 (4.0%)	12/50 (24.0%)
0	8	5	2	0	0		
1	1	24	3	2	0		
2	1	0	2	0	0		
3	0	0	0	0	0		
4	0	0	0	0	0		
Survodutide 4.8 mg						7/51 (13.7%)	15/51 (29.4%)
0	9	10	1	0	0		
1	4	17	3	1	0		
2	0	3	1	0	0		
3	0	0	0	1	0		
4	0	0	0	0	0		

Data are for the FAS according to planned maintenance doses

Safety

- There were no unexpected safety findings (**Table 3**)
- Overall, AEs occurred in 90.9% and 75.3% of survodutide 4.8 mg and placebo recipients, respectively (mainly GI: 81.8%, 41.6%)
- No survodutide recipients developed diabetes and more survodutide (78.5% across all doses) vs placebo recipients (28.6%) transitioned from pre-diabetes (HbA1c 5.7–6.5%) to normoglycemia (HbA1c <5.7%) by EoT

Table 3. Safety

n (%)	Survodutide 0.6 mg (n=77)	Survodutide 2.4 mg (n=78)	Survodutide 3.6 mg (n=77)	Survodutide 4.8 mg (n=77)	Placebo (n=77)
Any AE	70 (90.9)	70 (89.7)	71 (92.2)	70 (90.9)	58 (75.3)
Drug-related AE	47 (61.0)	66 (84.6)	62 (80.5)	62 (80.5)	29 (37.7)
Serious drug-related AE	0	0	2 (2.6)	0	0
AE leading to discontinuation	15 (19.5)	20 (25.6)	19 (24.7)	22 (28.6)	3 (3.9)
GI disorders[a]	44 (57.1)	67 (85.9)	58 (75.3)	63 (81.8)	32 (41.6)
Nausea	26 (33.8)	51 (65.4)	48 (62.3)	49 (63.6)	15 (19.5)
Vomiting	7 (9.1)	23 (29.5)	26 (33.8)	27 (35.1)	4 (5.2)
Diarrhea	14 (18.2)	22 (28.2)	18 (23.4)	15 (19.5)	8 (10.4)
Constipation	9 (11.7)	17 (21.8)	19 (24.7)	20 (26.0)	4 (5.2)
Type 2 diabetes	0	0	0	0	1 (1.3)

Data are for the treated set (all randomized participants who received ≥1 dose of study drug) according to planned maintenance doses
[a]GI disorders occurring in >10% of participants in the combined survodutide group

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Abbreviations
AE, adverse event; BMI, body mass index; CMDS, Cardiometabolic Disease Staging; EOSS, Edmonton Obesity Staging System; EoT, end of treatment; FAS, full analysis set; FPG, fasting plasma glucose; GCGR, glucagon receptor; GI, gastrointestinal; GLP-1R, glucagon-like peptide-1 receptor; HbA1c, glycated hemoglobin; SD, standard deviation

References
1. Del Prato S, et al. *Obesity Rev.* 2022;23:e13372. 2. Zimmermann T, et al. *Mol Metab.* 2022;66:101633. 3. Le Roux CW, et al. *Lancet Diabetes Endocrinol.* 2024;12:162. 4. Sharma A & Kushner R. *Int J Obes.* 2009;33:289. 5. Guo F, et al. *Obesity.* 2014;22:110.

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