Subgroup analysis by gender and body mass index (BMI) in people living with overweight/obesity in the survodutide, a glucagon/GLP-1 receptor dual agonist, phase II trial

Carel W. le Roux,[1] Oren Steen,[2] Kathryn J. Lucas,[3] Elena Startseva,[4] Anna Unseld,[5] Anita M. Hennige[6]

[1]St. Vincent's University Hospital and University College Dublin School of Medicine, Dublin, Ireland; [2]Private Practice, Toronto, ON, Canada; [3]Diabetes & Endocrinology Consultants PC, Morehead City, NC, USA; [4]Boehringer Ingelheim International GmbH, Ingelheim, Germany; [5]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; [6]Boehringer Ingelheim International GmbH, Biberach, Germany

Objective

- To explore the effects of gender and BMI on weight loss and AEs with survodutide in people living with overweight/obesity

Conclusions

- After 46 weeks of survodutide treatment, females appeared to lose more body weight and had a greater reduction in waist circumference than males
- Participants with a lower baseline BMI lost proportionally more body weight than those with a higher baseline BMI; whereas the trend was reversed for the reduction in waist circumference
- Plasma concentrations of survodutide will be investigated as one of the possible explanations for the differential weight loss between males and females, and between the highest and lowest baseline BMI subgroups
- The tolerability profile of survodutide was similar to that of GLP-1R mono-agonists and glucose-dependent insulinotropic polypeptide–GLP-1R dual agonists, with GI disorders being the most frequent drug-related AEs[8]
  - Treatment discontinuation was more common in participants receiving survodutide than PBO, which could be expected, given the rate of GI AEs reported with survodutide; however, data suggest that the discontinuation rate for participants reaching the target maintenance dose of 4.8 mg survodutide is similar to that for other GLP-1R–based therapies[8]

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Introduction

- Obesity is a complex, chronic, relapsing disease caused by dysregulation of energy input and expenditure,[1,2] and is associated with numerous comorbid diseases[3]
- Gender-related differences have been reported regarding obesity prevalence, comorbidities and response to GLP-1R agonists[4-6]
- The pathophysiology of obesity is complex, and agents that target multiple mechanisms may be more effective in reducing body weight than single-target agents,[7] such as GLP-1R agonists
- Survodutide is a GCGR/GLP-1R dual agonist in clinical development for chronic weight management in people living with obesity. In a phase II clinical trial in individuals with obesity without diabetes (NCT04667377), survodutide elicited up to 18.7% mean reduction in body weight after 46 weeks (primary endpoint) according to actual treatment[8]

Methods

- Data for this post hoc analysis were derived from a multinational 46-week randomized, double-blind, PBO-controlled, dose-finding phase II trial (ClinicalTrials.gov, NCT04667377; EudraCT, 2020–002479–37)[8]
  - 387 adults with BMI ≥27 kg/m² without diabetes were randomized 1:1:1:1:1 to weekly subcutaneous survodutide (0.6, 2.4, 3.6, or 4.8 mg) or PBO over 46 weeks
  - An initial 20-week rapid dose-escalation period (adjusted for GI tolerability), was followed by a 26-week dose-maintenance period
- Participants also received dietary and physical activity counselling
- Percentage change in body weight (primary endpoint), absolute change in body weight and waist circumference (secondary endpoints), and AEs were assessed in subgroups based on gender and BMI at baseline
- Data were analyzed descriptively for all participants who received ≥1 dose of study drug and had data for ≥1 efficacy endpoint, according to doses assigned at randomization (planned treatment); FAS n=384

Results

- Of 384 participants, 68.2% were female and 31.8% were male; at baseline, 9.9%, 30.5% , 31.8% and 27.9% had a BMI of <30, 30 to <35, 35 to <40, and ≥40 kg/m², respectively
- Demographics and clinical characteristics at baseline were similar between males and females, and across BMI subgroups (data not shown)

Primary and key secondary endpoints by gender and BMI

- At Week 46, mean percentage change in body weight from baseline with survodutide 4.8 mg vs PBO was −11.9% vs −3.3% in males and −17.0% vs −3.2% in females (**Figure 1A**), and −19.1% vs −1.7%, −15.8% vs −3.1%, −15.4% vs −5.8%, and −13.4% vs −0.8% in participants with a BMI of <30, 30 to <35, 35 to <40, and ≥40 kg/m², respectively (**Figure 1B**)

Figure 1A. Percentage change in body weight from baseline to Week 46 by gender (FAS, planned treatment)

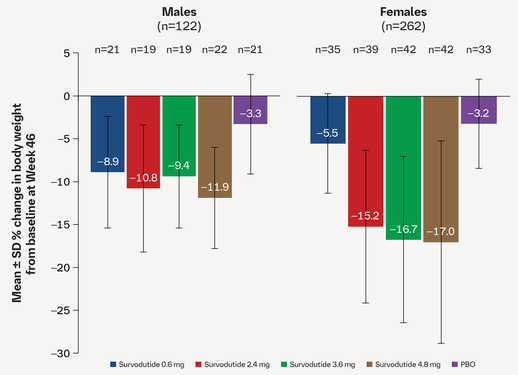
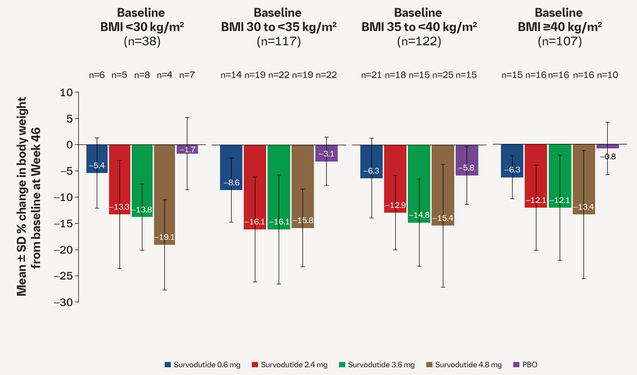


Figure 1B. Percentage change in body weight from baseline to Week 46 by BMI at baseline (FAS, planned treatment)



- Mean absolute change in waist circumference from baseline with survodutide 4.8 mg vs PBO was −12.8 vs −1.7 cm in males and −17.9 vs −4.9 cm in females (**Figure 2A**); and for BMI subgroups was −8.4 vs −2.6 cm, −14.3 vs −6.4 cm, −17.5 vs −5.0 cm, and −17.2 vs 3.3 cm in participants with a BMI of <30, 30 to <35, 35 to <40, and ≥40 kg/m², respectively (**Figure 2B**)

Figure 2A. Absolute change in waist circumference from baseline to Week 46 by gender (FAS, planned treatment)

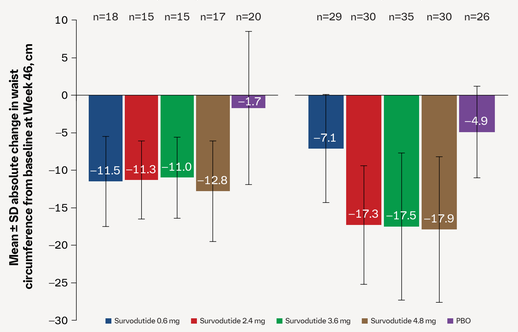
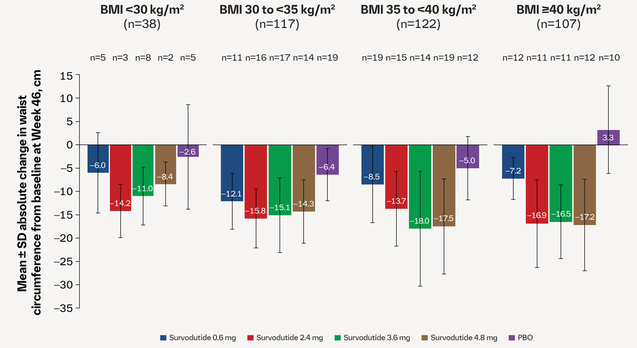


Figure 2B. Absolute change in waist circumference from baseline to Week 46 by BMI at baseline (FAS, planned treatment)



For all figures: n at baseline shown in gender or BMI category; n at Week 46 shown in treatment group
Planned treatment was defined as the maintenance dose assigned at randomization, and included all data censored for COVID-19–related treatment discontinuations

Safety by gender and BMI

- All survodutide doses (pooled data) were tolerated as expected across gender and baseline BMI subgroups (**Table 1**); rates of AEs, serious AEs and discontinuations were comparable in males and females, and across BMI subgroups
- GI AEs with all survodutide doses were experienced by fewer males (65.7%) than females (79.5%); nausea was the most frequently reported GI AE in males and females, and across BMI subgroups

Table 1. Summary of AEs by gender and by baseline BMI (TS, planned treatment)

	Male (n=123)		Female (n=263)		BMI <30 kg/m² (n=39)		BMI 30 to <35 kg/m² (n=118)		BMI 35 to <40 kg/m² (n=122)		BMI ≥40 kg/m² (n=107)	
AE, n (%)	Survodutide pooled (n=99)	PBO (n=24)	Survodutide pooled (n=210)	PBO (n=53)	Survodutide pooled (n=30)	PBO (n=9)	Survodutide pooled (n=90)	PBO (n=28)	Survodutide pooled (n=98)	PBO (n=24)	Survodutide pooled (n=91)	PBO (n=16)
Any AE	87 (87.9)	21 (87.5)	194 (92.4)	37 (69.8)	26 (86.7)	8 (88.9)	83 (92.2)	22 (78.6)	90 (91.8)	16 (66.7)	82 (90.1)	12 (75.0)
GI disorders	65 (65.7)	9 (37.5)	167 (79.5)	23 (43.4)	16 (53.3)	7 (77.8)	72 (80.0)	9 (32.1)	76 (77.6)	7 (29.2)	68 (74.7)	9 (56.3)
Nausea	43 (43.4)	2 (8.3)	131 (62.4)	13 (24.5)	14 (46.7)	4 (44.4)	58 (64.4)	5 (17.9)	56 (57.1)	3 (12.5)	46 (50.5)	3 (18.8)
Vomiting	15 (15.2)	0 (0.0)	68 (32.4)	4 (7.5)	9 (30.0)	2 (22.2)	29 (32.2)	0 (0.0)	22 (22.4)	0 (0.0)	23 (25.3)	2 (12.5)
Diarrhea	20 (20.2)	1 (4.2)	49 (23.3)	7 (13.2)	1 (3.3)	2 (22.2)	23 (25.6)	3 (10.7)	26 (26.5)	1 (4.2)	19 (20.9)	2 (12.5)
Constipation	19 (19.2)	1 (4.2)	46 (21.9)	3 (5.7)	2 (6.7)	0 (0.0)	16 (17.8)	1 (3.6)	25 (25.5)	1 (4.2)	22 (24.2)	2 (12.5)
Leading to discontinuation	25 (25.3)	0 (0.0)	51 (24.3)	3 (5.7)	5 (16.7)	1 (11.1)	22 (24.4)	0 (0.0)	22 (22.4)	2 (8.3)	27 (29.7)	0 (0.0)
Serious AE	4 (4.0)	1 (4.2)	9 (4.3)	4 (7.5)	0 (0.0)	1 (11.1)	3 (3.3)	1 (3.6)	4 (4.1)	2 (8.3)	6 (6.6)	1 (6.3)
Investigator defined, drug-related	72 (72.7)	8 (33.3)	165 (78.6)	21 (39.6)	16 (53.3)	6 (66.7)	76 (84.4)	8 (28.6)	78 (79.6)	7 (29.2)	67 (73.6)	8 (50.0)
Serious AE, investigator defined,drug-related	1 (1.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.2)	0 (0.0)

Data shown are for all randomized participants who received ≥1 dose of trial treatment, based on planned treatment, including on-treatment data only (N=386)
Pooled refers to data from all survodutide dose groups combined

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Abbreviations
AE, adverse event; BMI, body mass index; FAS, full analysis set; GCGR, glucagon receptor; GI, gastrointestinal; GLP-1R, glucagon-like peptide-1 receptor; PBO, placebo; SD, standard deviation; TS, treated set

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