A phase II, randomized, double-blind, placebo-controlled, dose-finding study of survodutide (BI 456906) in people living with overweight/obesity

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Objective

- To evaluate the efficacy and safety of survodutide across a range of doses in participants with overweight/obesity

Methods

- This was a 46-week multinational, randomized, double-blind, parallel group, placebo-controlled dose-finding phase II trial (NCT04667377) conducted in adults with body mass index (BMI) ≥27 kg/m² and without diabetes
- Participants were randomized 1:1:1:1:1 to weekly subcutaneous survodutide (4 dose groups: 0.6, 2.4, 3.6, and 4.8 mg) or placebo, n≈77 per arm. The 46-week treatment period comprised a 20-week dose escalation phase (increases every 2 weeks) plus a 26-week maintenance phase (fixed dose)
- The primary endpoint was bodyweight change (%) from baseline to Week 46
- Secondary endpoints included absolute change in bodyweight, waist circumference, systolic blood pressure (SBP), and diastolic blood pressure (DBP) from baseline to Week 46
- A mixed model for repeated measurements was used for analysis
- Primary and sensitivity analyses were based on different treatment sets
  - The primary analysis was based on the maintenance dose **planned treatment** and included all data censored for COVID-19–related discontinuations
    - Planned treatment was the maintenance dose assigned to participants at the time of randomization
  - The sensitivity analysis was based on the actual treatment and included on-treatment data only
    - Actual treatment was the actual dose that participants received during the maintenance phase
- Secondary endpoint analyses were based on planned treatment and on-treatment data only

Results

Baseline demographics and clinical characteristics were similar between study arms

Parameter	Survodutide 0.6 mg (n=77)	Survodutide 2.4 mg (n=78)	Survodutide 3.6 mg (n=76)	Survodutide 4.8 mg (n=76)	Placebo (n=77)	Total (N=384)
Sex, n (%)						
Female	51 (66.2)	54 (69.2)	51 (67.1)	53 (69.7)	53 (68.8)	262 (68.2)
Age, years	48.6 ± 12.6	49.0 ± 13.1	50.3 ± 11.8	47.6 ± 13.5	50.0 ± 13.5	49.1 ± 12.9
Race, n (%)						
White	59 (76.6)	60 (76.9)	63 (82.9)	59 (77.6)	60 (77.9)	301 (78.4)
BMI, kg/m²	37.8 ± 6.3	37.6 ± 7.3	37.0 ± 5.7	37.6 ± 6.0	35.8 ± 5.0	37.1 ± 6.1
Weight, kg	107.0 ± 18.7	106.6 ± 23.0	104.7 ± 19.6	105.9 ± 17.4	104.3 ± 22.9	105.7 ± 20.4
Waist circumference, cm	115.3 ± 13.4	115.3 ± 17.0	112.8 ± 13.9	112.8 ± 13.0	110.4 ± 14.6	113.4 ± 14.5
SBP, mmHg	125.0 ± 13.4	125.4 ± 13.3	127.4 ± 13.2	122.6 ± 12.3	127.5 ± 14.2	125.6 ± 13.4
DBP, mmHg	80.5 ± 7.5	80.7 ± 7.4	81.8 ± 8.1	80.8 ± 7.6	82.4 ± 8.6	81.3 ± 7.8
Hypertension, n (%)*	32 (34.8)	30 (32.6)	29 (40.8)	18 (33.3)	25 (32.5)	134 (34.7)

Data shown as mean ± SD unless otherwise stated.
Data from the full analysis set (all randomized patients who received ≥1 dose and had analyzable data for ≥1 efficacy endpoint).
*Data from the treated set, all randomized patients who received ≥1 dose of medication (n=386).
BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation

Survodutide (BI 456906), a dual glucagon receptor (GCGR)/glucagon-like peptide-1 receptor (GLP-1R) agonist, reduced bodyweight and improved cardiometabolic outcomes after 46 weeks, with no unexpected safety concerns

What was known

- The bodyweight-lowering effects of GCGR agonism (increasing energy expenditure) and GLP-1R agonism (decreasing energy intake) are additive[1–3]
- Survodutide (BI 456906) is a novel, subcutaneous, once-weekly GCGR/GLP-1R dual agonist in development for the treatment of obesity and non-alcoholic steatohepatitis[4,5]

What's new

- In a phase II, randomized, controlled trial, survodutide treatment resulted in mean bodyweight reductions of up to 18.7%. Up to 40% of participants receiving survodutide achieved bodyweight reductions of ≥20% after 46 weeks of treatment
- Survodutide reduced waist circumference and blood pressure, with no unexpected safety findings
- Survodutide appears to be a promising new anti-obesity treatment and will be further investigated in phase III clinical trials

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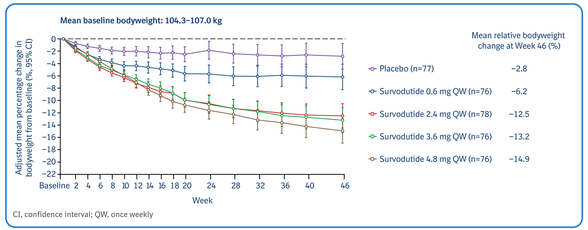
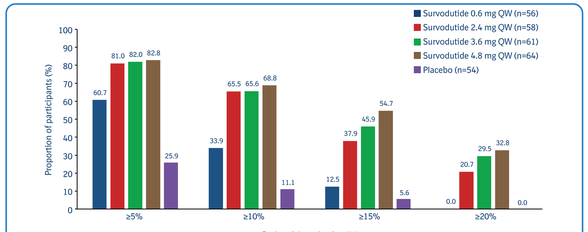
Survodutide treatment (planned) dose-dependently reduced bodyweight up to 14.9% over 46 weeks



CI, confidence interval; QW, once weekly

- Treatment with survodutide (actual) resulted in dose-dependent reduction in bodyweight up to 18.7% versus 2.0% with placebo over 46 weeks
- Treatment with survodutide (actual) dose-dependently reduced absolute bodyweight up to 19.5 kg versus 2.7 kg with placebo over 46 weeks

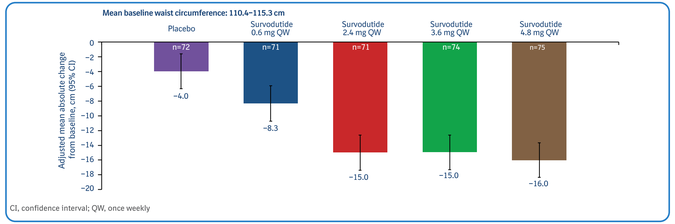
Up to one-third of participants (planned treatment) achieved ≥20% bodyweight reduction with survodutide treatment at Week 46



QW, once weekly

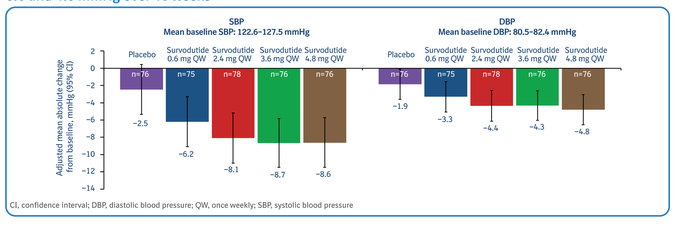
- Up to 40% of participants on actual treatment experienced ≥20% bodyweight reduction with survodutide treatment at Week 46

Survodutide treatment (planned) reduced absolute waist circumference up to 16.0 cm over 46 weeks



CI, confidence interval; QW, once weekly

Survodutide treatment (planned) reduced absolute systolic and diastolic blood pressure up to 8.6 and 4.8 mmHg over 46 weeks



CI, confidence interval; DBP, diastolic blood pressure; QW, once weekly; SBP, systolic blood pressure

Treatment with survodutide was tolerable, with no unexpected safety findings. Most treatment discontinuations occurred during the rapid dose escalation phase (up to Week 20)

TEAE, 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)	Survodutide total (n=309)	Placebo (n=77)
Any TEAE	70 (90.9)	70 (89.7)	71 (92.2)	70 (90.9)	281 (90.9)	58 (75.3)
Nausea†	26 (33.8)	51 (65.4)	48 (62.3)	49 (63.6)	174 (56.3)	15 (19.5)
Vomiting†	7 (9.1)	23 (29.5)	26 (33.8)	27 (35.1)	83 (26.9)	4 (5.2)
Diarrhea†	14 (18.2)	22 (28.2)	18 (23.4)	15 (19.5)	69 (22.3)	8 (10.4)
Constipation†	9 (11.7)	17 (21.8)	19 (24.7)	20 (26.0)	65 (21.0)	4 (5.2)
Leading to treatment discontinuation	15 (19.5)	20 (25.6)	19 (24.7)	22 (28.6)	76 (24.6)	3 (3.9)
GI-related	5 (6.5)	13 (16.7)	13 (16.9)	20 (26.0)	51 (16.5)	1 (1.3)
Serious	1 (1.3)	2 (2.6)	6 (7.8)	4 (5.2)	13 (4.2)	5 (6.5)
Investigator defined, drug-related TEAE	47 (61.0)	66 (84.6)	62 (80.5)	62 (80.5)	237 (76.7)	29 (37.7)
Serious, drug-related	0 (0.0)	0 (0.0)	2 (2.6)	0 (0.0)	2 (0.6)	0 (0.0)

*Based on the treated set and presented according to planned treatment. †TEAEs listed according to preferred term occurred in ≥15% patients in any one trial arm.
GI, gastrointestinal; TEAE, treatment-emergent adverse event

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