The dual glucagon/GLP-1 receptor agonist survodutide improved cardiovascular risk biomarkers in adults with obesity in a phase 2 trial

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Objective

- To analyze molecular markers of cardiometabolic health and cardiovascular risk in the randomized phase 2 trial of survodutide for obesity[1]

Conclusions

- In people living with obesity or overweight, treatment with survodutide was associated with improvements in molecular markers of adiposity, inflammation, insulin resistance, and atherosclerosis
- Mechanisms may involve indirect (via weight reduction) or direct effects of dual glucagon receptor/GLP-1 receptor agonism, e.g., anti-inflammatory effects of glucagon[2] and GLP-1[3] signaling
- Overall, these changes suggest survodutide may decrease cardiovascular risk and improve cardiometabolic health in people living with obesity

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Introduction

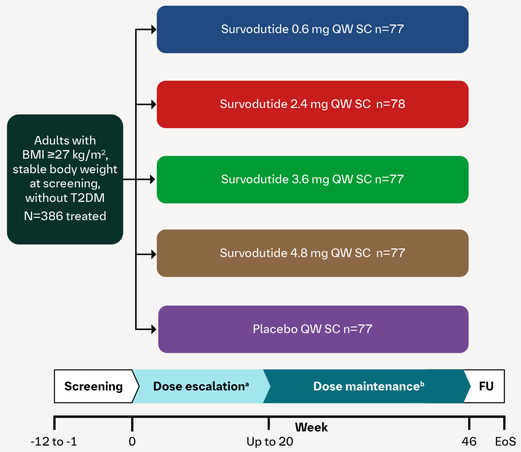
- GCGR agonism combined with GLP-1R agonism may enhance body weight reduction and have direct hepatoprotective effects[4]
- Survodutide is a unimolecular dual GCGR/GLP-1R agonist in phase 3 clinical trials for treatment of obesity (SYNCHRONIZE™)[5] or MASH (LIVERAGE™)[6]
- In a randomized phase 2 trial, survodutide elicited up to 18.7% mean reduction in body weight after 46 weeks of treatment[a] (the primary endpoint) in people living with obesity or overweight without diabetes[1]

[a]According to actual maintenance doses.

Methods

- The trial design is shown in **Figure 1**.

Figure 1. Trial design



[a]In Weeks 11–20, tolerability was assessed every 2 weeks; if GI AEs were intolerable, participant remained on the same dose for another week before dose escalation.

[b]Participants who did not tolerate treatment due to GI AEs during dose escalation could remain on a lower survodutide dose (than the dose allocated to them at randomization) for the duration of the maintenance phase. Participants who could not tolerate the lowest survodutide dose tested (0.6 mg) despite all the efforts taken discontinued treatment.

- Changes from baseline over time were analyzed for plasma levels of multiple biomarkers including leptin, ICAM-1, apolipoprotein A, CRP, E-selectin, PEDF, coagulation factor VII, CCL18, P-selectin, PAI-1, and IL-18 in a prespecified analysis
- Multiplex assay platform (Luminex 100/200™ xMAP) was used to simultaneously detect and quantitate multiple secreted proteins using ProcartaPlex assays
- Data were analyzed with MMRM for all participants receiving ≥1 dose of trial drug with data for ≥1 efficacy endpoint (i.e., full analysis set) according to doses received during maintenance using on-treatment data
- Data reported were on-treatment data by actual treatment for the full analysis set from MMRM with main effects for treatment, baseline and visit and interaction terms for treatment by visit and baseline by visit, and unstructured covariance matrix structure for repeated measurements within participants

Results

- Baseline demographic and clinical characteristics were similar between treatment groups

Table 1. Baseline demographics and characteristics

	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)
Sex, n (%)					
Female	51 (66.2)	54 (69.2)	51 (67.1)	53 (69.7)	53 (68.8)
Age, years	48.6 ± 12.6	49.0 ± 13.1	50.3 ± 11.8	47.6 ± 13.5	50.0 ± 13.5
Race, n (%)					
White	59 (76.6)	60 (76.9)	63 (82.9)	59 (77.6)	60 (77.9)
Asian	8 (10.4)	9 (11.5)	9 (11.8)	7 (9.2)	7 (9.1)
Black	10 (13.0)	8 (10.3)	3 (3.9)	8 (10.5)	8 (10.4)
BMI, kg/m²	37.8 ± 6.3	37.6 ± 7.3	37.0 ± 5.7	37.6 ± 6.0	35.8 ± 5.0
Weight, kg	107.0 ± 18.7	106.6 ± 23.0	104.7 ± 19.6	105.9 ± 17.4	104.3 ± 23.0
n	69	72	69	72	71
Leptin, µg/L	45 ± 31	43 ± 26	42 ± 28	52 ± 41	44 ± 27
ICAM-1, µg/L	93 ± 27	90 ± 25	92 ± 30	94 ± 34	87 ± 24
E-selectin, µg/L	7.6 ± 2.5	7.7 ± 2.9	7.0 ± 3.1	7.3 ± 4.0	6.9 ± 2.6
Apolipoprotein A, mg/L	205 ± 242	265 ± 354	179 ± 207	300 ± 374	231 ± 298
CRP, mg/L	6.6 ± 15.3	5.6 ± 8.5	5.3 ± 8.7	6.3 ± 9.9	4.0 ± 5.0
PEDF, µg/L	6325 ± 1754	5951 ± 1399	6160 ± 1390	5883 ± 1438	5915 ± 1687
Coagulation factor VII, µg/L	706 ± 244	705 ± 258	641 ± 250	675 ± 249	709 ± 241
CCL18, µg/L	134 ± 66	139 ± 61	124 ± 56	134 ± 60	132 ± 62

Unless otherwise stated, data for demographic and clinical characteristics are mean ± standard deviation for the full analysis set according to planned maintenance doses. Data for biomarkers are for the full analysis set using on-treatment data.

Change in CRP, PEDF, coagulation factor VII, and CCL18 at Week 46

- Decreases in CRP, PEDF, Factor VII, and CCL18 with survodutide 2.4 mg, 3.6 mg, and 4.8 mg suggest reductions in inflammation, atherosclerosis, insulin resistance, and prothrombotic state
- No significant changes in P-selectin, PAI-1, or IL-18 were observed

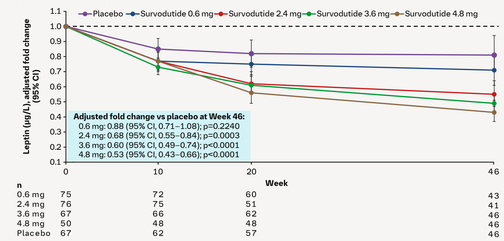
Table 2. Placebo-adjusted fold change in biomarker data at Week 46 (95% CI)

	Survodutide 0.6 mg (n=77)	Survodutide 2.4 mg (n=78)	Survodutide 3.6 mg (n=76)	Survodutide 4.8 mg (n=76)
CRP	0.80 (0.57–1.14) p=0.2160	0.52 (0.36–0.74) p=0.0003	0.54 (0.38–0.76) p=0.0004	0.60 (0.42–0.86) p=0.0048
PEDF	0.97 (0.91–1.04) p=0.4514	0.91 (0.85–0.98) p=0.0112	0.88 (0.83–0.95) p=0.0005	0.87 (0.81–0.93) p=0.0001
Factor VII	0.93 (0.85–1.02) p=0.1295	0.87 (0.79–0.96) p=0.0053	0.83 (0.76–0.91) p=0.0001	0.83 (0.75–0.91) p=0.0001
CCL18	0.94 (0.87–1.01) p=0.1109	0.89 (0.83–0.96) p=0.0033	0.88 (0.82–0.95) p=0.0010	0.87 (0.81–0.94) p=0.0005

Improved cardiovascular risk biomarkers over time

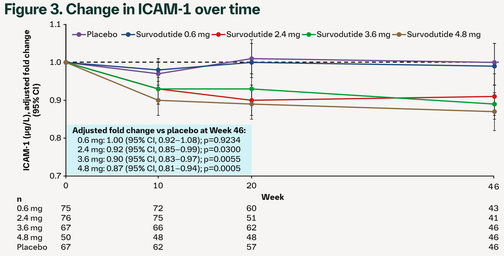
- Significant decreases in leptin were observed in the 2.4 mg, 3.6 mg, and 4.8 mg survodutide groups compared with placebo (**Figure 2**); leptin reductions may reflect reduced adiposity

Figure 2. Change in leptin over time



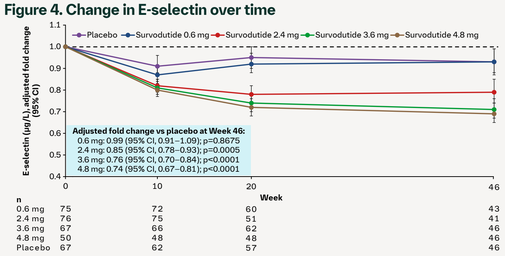
- Significant reductions in ICAM-1 were observed in the 2.4 mg, 3.6 mg, and 4.8 mg survodutide groups compared with placebo (**Figure 3**); decreased ICAM-1 suggests reduced inflammation and improved endothelial function

Figure 3. Change in ICAM-1 over time



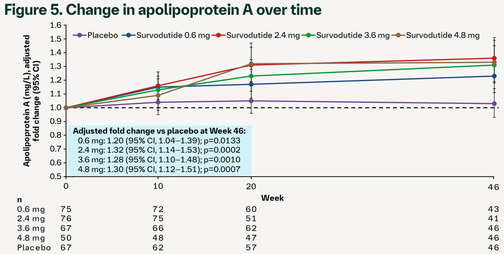
- Significant reductions in E-selectin were observed in the 2.4 mg, 3.6 mg, and 4.8 mg survodutide groups compared with placebo (**Figure 4**); decreased E-selectin suggests reduced inflammation and improved endothelial function

Figure 4. Change in E-selectin over time



- Significant increases in apolipoprotein A were observed in all survodutide groups compared with placebo (**Figure 5**); increases in apolipoprotein A may indicate reduced atherosclerosis

Figure 5. Change in apolipoprotein A over time



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Abbreviations
AE, adverse event; BMI, body mass index; CI, confidence interval; CCL, chemokine ligand; CRP, C-reactive protein; EoS, end of study; FU, follow-up; GI, gastrointestinal; GCGR, glucagon receptor; GLP-1, glucagon-like peptide-1 receptor; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; MASH, metabolic dysfunction-associated steatohepatitis; MMRM, mixed model for repeated measures; PAI, plasminogen activator inhibitor; PEDF, pigment epithelium-derived factor; SC, subcutaneous; T2DM, type 2 diabetes mellitus; QW, once weekly

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Disclosures
MB has received honoraria as a consultant and speaker from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Lilly, Novartis, Novo Nordisk, Pfizer, and Sanofi; and has participated on a data safety monitoring board/advisory board for Boehringer Ingelheim. **SGM**, **AMH**, **ES**, and **CS** are employees of Boehringer Ingelheim.

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