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Review Article

Survodutide, a new horizon in the treatment of obesity and Type 2 diabetes mellitus: A narrative review

Abdelmoneim B. Yousif[1]*, Ebtihal Abdelmoneim Hassan[2], Mohamed Fawzi Mudarres[3], Musaab Fahmi Yousef[4]

[1]*Dept. of Pharmacy, Hamad General Hospital, Doha, Qatar*
[2]*Dept. of Accident & Emergency, Hamad General Hospital, Doha, Qatar*
[3]*University of Lowa Hospitals and Clinics, Doha, Qatar*
[4]*Dept. of Medicine, University of Jordan, School of Medicine, Amman, Jordan*

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ABSTRACT

The global increase in type 2 diabetes mellitus (T2DM) and obesity requires effective treatments. However, conventional antidiabetic drugs often result in weight gain, highlighting the need for novel therapies that treat both T2DM and obesity. Recently, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) RAs have been shown to be effective in weight loss and metabolic improvement. Survodutide (BI 456906) is an investigational long-acting double agonist administered weekly. Phase 2 trials exhibited significant reductions in HbA1c (up to 1.7% at 16 weeks) and substantial weight loss (up to 14.9% at 46 weeks) in patients with T2DM and obesity. In addition, survodutide enhanced cardiovascular risk factors and some markers of non-alcoholic steatohepatitis (NASH). However, notable rates of gastrointestinal side effects and treatment discontinuation have been observed. Future research should prioritize addressing these adverse effects and assessing long-term outcomes. The current review evaluated the efficacy and safety of survodutide, a novel dual GLP-1/GIP receptor agonist, in managing obesity and T2DM. Clinical and preclinical data on survodutide were analyzed, focusing on its mechanism of action, clinical trial results, and comparisons with other therapies.

1. Introduction

Type 2 diabetes mellitus (T2DM) and obesity are closely linked and are increasing in prevalence worldwide, with significant implications for the global health economy. A range of treatment options are available for people with obesity and T2DM, including low-calorie diets, medications, and bariatric surgery. Obesity should be considered when choosing medical therapy for T2DM, as common antidiabetic medications may result in weight gain.[1] In recent years, newer therapeutic agents have proliferated, revolutionizing the treatment landscape for T2DM and obesity. In particular, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), including semaglutide, liraglutide, and the recently approved dual GLP-1/ glucose-dependent insulinotropic polypeptide (GIP) RA agonist tirzepatide, have been shown to be effective drugs not only promoting weight loss but also enhancing metabolic parameters such as lipid profiles, glucose levels, and central adiposity.[2]

Survodutide (BI 456906) is an investigational long-acting, GIP/GLP-1 receptor dual agonist whose safety and efficacy have not been approved for marketing by any regulatory authority.[3] Survodutide was previously assessed

* *Corresponding author.*
E-mail address: mabdelmonem209@gmail.com (A. B. Yousif).

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in three phase 2 clinical trials. The first was a phase 2 trial with survodutide in people with T2DM on stable metformin background therapy and showed dose-dependent reductions in blood sugar, and hemoglobin A1c (HbA1c), after 16 weeks. The second was a phase 2 trial with survodutide in people living with overweight or obesity and demonstrated dose-dependent body weight reductions after 46 weeks. The third was a phase 2 trial with survodutide in people with metabolic dysfunction-associated steatohepatitis (MASH) and showed improvements in MASH and liver fibrosis after 48 weeks. MASH is one of the most prevalent and serious obesity-related comorbidities.[3] The current review aimed to evaluate the efficacy and safety of survodutide, a novel dual GIP/GLP-1 receptor agonist, in managing obesity and T2DM. Clinical and preclinical data on survodutide were analyzed, focusing on its mechanism of action, clinical trial results, and comparisons with other therapies.

2. Survodutide

Survodutide (BI 456906) is an investigational long-acting, dual GIP/GLP-1 receptor agonist for once-weekly subcutaneous administration. The molecule is designed to leverage the body weight reduction and glycemic control of GLP-1 receptors with some activity on the glucagon receptors, which are present in the liver.[3] In phase 2 trials, good glycemic control and striking weight reduction were demonstrated.[4]

2.1. Chemical components and mechanism of action

The natural hormone oxyntomodulin acts as a weak agonist of both the GLP-1 receptor (GLP-1R) and the glucagon receptor (GCGR), demonstrating brief efficacy in reducing body weight and blood glucose levels by increasing energy expenditure and decreasing energy intake in humans, albeit for a short period of time, due to its short half-life.[5] Survodutide (BI 456906) is a synthetic compound that mimics the natural hormone oxyntomodulin but has a prolonged half-life. It is a potent 29-amino acid acylated peptide containing a C18 fatty acid as a half-life prolonging agent to support once-weekly administration in humans.[6–8] Moreover, unlike oxyntomodulin, survodutide is resistant to enzymatic degradation by dipeptidyl peptidase-4.[7]

Survodutide acts as a dual agonist of the glucagon and GLP-1 receptors (GCGR and GLP-1R), pivotal for regulating metabolic functions. This dual action aims to improve weight loss efficacy beyond that of GLP-1R agonists by reducing energy intake and enhancing energy expenditure, addressing fundamental principles of energy balance critical for body weight regulation.[7]

2.2. Trials

2.2.1. Survodutide effects on HbA1c in people with type 2 diabetes mellitus

In a randomized, partly double-blind, phase 2 trial, different doses of survodutide (0.3, 0.9, 1.8, and 2.7 mg once weekly and 1.2 mg and 1.8 mg twice weekly) were compared with open-label semaglutide 1.0 mg once weekly and placebo in patients with type 2 diabetes.[9] The study included 411 patients (44% women, mean age 57.3 years, mean body mass index [BMI] 33.9 kg/m^2, and mean HbA1c 8.1%), all of whom were receiving metformin.[9] Participants were randomized into groups of approximately 50 subjects each, except for the placebo group (n=59). The primary endpoint was the change in HbA1c levels from baseline to 16 weeks.[9] The smallest dose of survodutide (0.3 mg/week) resulted in a mean HbA1c reduction of 0.9%, while higher doses achieved a significant reduction in HbA1c ranging from 1.5% to 1.7%, without a clear dose-response relationship.[9] The HbA1c reduction in the survodutide groups (except for the lowest dose) was similar to the 1.5% reduction observed in the semaglutide group.[9] On the contrary, the placebo group experienced a minimal HbA1c reduction of approximately 0.2%.[9] Analysis of HbA1c changes over time suggested that reductions with survodutide plateaued at 16 weeks, whereas reductions with semaglutide did not.[9] However, a longer duration of therapy is needed to confirm this observation.

2.2.2. b survodutide effects on body weight reduction in obese people

A second randomized, double-blind phase 2 trial examined the effects of survodutide on weight loss in obese subjects without diabetes.[4] The study included 384 subjects (68% women, mean age 49 years, mean BMI 37.1 kg/m^2, and mean weight 105.7 kg) who were randomized to receive weekly doses of survodutide (0.6 mg, 2.4 mg, 3.6 mg, and 4.8 mg) or placebo, in addition to dietary and physical activity counseling.[4] The trial consisted of two phases: an initial 20-week dose escalation phase and a 26-week dose maintenance phase.[4]

At 46 weeks, the primary endpoint was mean percentage weight loss from baseline. The intervention groups showed significant weight reduction, ranging from 6.2% (95% CI 4.1–8.3) with survodutide 0.6 mg to 14.9% (95% CI 13.0–16.9) with survodutide 2.4 mg, in comparison to 2.8% (95% CI 0.7–4.9) with placebo.[4] A secondary endpoint, weight loss of 10%, was achieved by 69% of subjects with survodutide 4.8 mg in comparison to 11% with placebo.[4]

In the diabetes study by Blüher et al.[9], weight reduction was a secondary endpoint. After 16 weeks, survodutide 1.8 mg/week was associated with mean relative weight reduction of 8.7% (95% CI 7.3–10.1).[9] Weight loss with survodutide doses 1.8 mg/week was significantly greater than the 5.3% (95% CI 4.1–6.6) weight reduction

achieved by semaglutide at 16 weeks. In both trials, weight loss with survodutide continued progressively up to the end of the intervention without evidence of reaching a plateau.[4,9] In experiments, survodutide exhibited balanced dual GCGR/GLP-1R pharmacology, achieving superior weight loss efficacy in comparison to selective GLP-1R agonists while maintaining similar antidiabetic benefits.[10]

2.2.3. Survodutide effects on reducing cardiovascular risk factors

In comparison with placebo, survodutide 3.6 mg/week was associated with significant reductions in both systolic and diastolic blood pressure by 6.2 mmHg and 2.9 mmHg, respectively[4]. Moreover, significant reductions in plasma concentrations of triglycerides and very low-density lipoprotein cholesterol (VLDL-C) by approximately 28% were observed with the 2.4 mg and 3.6 mg doses of survodutide, in comparison to a 5% increase with placebo.[4] No significant effects were observed on other plasma lipids with survodutide.[4]

2.2.4. Survodutide effects on biomarkers of non-alcoholic fatty liver diseases

Recently, non-alcoholic fatty liver disease (NAFLD) has been recognized as a major health problem associated with obesity and T2DM. NAFLD consists of various entities, ranging from non-alcoholic fatty liver to non-alcoholic steatohepatitis (NASH). Given its effects on weight loss and the potential stimulation of fatty acid oxidation in the liver through glucagon agonism[6], there was interest in exploring the effects of survodutide for the management of NASH.[6] Survodutide treatment led to improvements in some biomarkers of NASH, including the enhanced liver fibrosis score and pro-C3. However, no significant effects were observed on other NASH-related markers, including the Fib-4 score, aspartate aminotransferase/platelet ratio, and non-alcoholic fatty liver disease (NAFLD) score.[9]

2.3. Survodutide versus semaglutide and tirzepatide

In recent trials, survodutide has shown promising results in weight management. A 46-week study of once-weekly survodutide (0.6 to 4.8 mg) demonstrated dose-dependent weight loss up to 18.7% in obese individuals, significantly outperforming the 2% weight loss observed with placebo[4]. For individuals with type 2 diabetes (T2D), survodutide administered at 1.8 mg twice weekly resulted in a 9% weight loss over 16 weeks, surpassing the 5.4% achieved with semaglutide 1 mg and the 1.2% with placebo in a similar trial.

In comparison, tirzepatide, a dual receptor agonist for GLP-1 and GIP, yielded robust outcomes in glycemic control and weight reduction. The SURPASS program reported a mean HbA1c reduction of 1.9–2.6% and achieved 10% weight loss in 40–69% of participants with higher doses (10 and 15 mg).[11,12] Notably, tirzepatide indicated superior efficacy in reducing glycated hemoglobin levels and promoting weight loss in comparison to semaglutide.[12] In separate trials, SURMOUNT-1 documented 16–22.5% weight loss over 72 weeks in non-diabetic individuals, contrasting with a 2.4% weight loss in the placebo group.[13] Similarly, SURMOUNT-2 exhibited a substantial 15.7% weight loss with tirzepatide 15 mg versus 3.3% with placebo in obese individuals with T2D.[14] In the SURMOUNT-4 study, the mean percent weight change from week 36 to week 88 was 5.5% with tirzepatide in comparison to 14.0% with placebo ($P < 0.001$). Overall, the mean weight reduction from week 0 to 88 was 25.3% for tirzepatide and 9.9% for placebo ($P < 0.001$).[7]

This comparative analysis underscores the potential of survodutide and tirzepatide as effective therapies for weight management and diabetes control, positioning them as promising alternatives to semaglutide in clinical practice.

2.4. Advantages of survodutide

Survodutide demonstrated effectiveness in lowering HbA1c levels by approximately 1.5–1.7% in patients with type 2 diabetes and achieving weight loss of approximately 12% in subjects with obesity.[4,9] As an anti-diabetic agent, survodutide exhibited comparable efficacy to submaximal doses of semaglutide 1.0 mg/week.[9] Semaglutide at its maximal dose of 2.4 mg/week may offer superior glycemic control in comparison to survodutide.

In terms of weight reduction, survodutide was significantly more effective than semaglutide 1.0 mg/week, with reductions of 6.6% and 5.3%, respectively.[9] However, results might differ in comparison to the highest dose of semaglutide of 2.4 mg/week. Survodutide also exhibited advantages in reducing blood pressure and plasma triglycerides, likely attributed to its effects on weight loss.[4] Notably, injection site reactions were not reported with survodutide administration.[4,9]

2.5. Limitations of survodutide

Survodutide demonstrated several notable limitations. Firstly, it is associated with high rates of gastrointestinal (GI) disorders and discontinuation rates ranging from 25% to 29%, notably higher than the 4% observed with placebo.[4] The rapid dose escalation of survodutide every two weeks likely contributes to these adverse effects.[4]

Secondly, studies revealed that women tend to respond more favorably to GLP-1-based drugs in terms of weight loss in comparison to men.[16,17] This gender disparity in weight loss response may stem from physiological and hormonal differences; women generally have higher estrogen levels, increased body fat, and a different fat distribution, enhancing the drug's efficacy.[18] Furthermore, variations in pharmacokinetics based on gender could

Table 1: Comparison between survodutide, cotadutide, semaglutide, and tirzepatide

Drug characteristic	Survodutide [4,9]	Semaglutide [9]	Tirzepatide [13–15]
Frequency of subcutaneous administration	Once weekly	Once weekly	Once weekly
Maximum HbA1c reduction	1.7% at 16 weeks	1.5% at 16 weeks	2.24% at 40 weeks [12] 1.87% to 3.02% at 104 weeks [11]
Maximum percent weight reduction	8.7% at week 16 [9] 149% at 46 weeks [4]	5.3% at week 16	25.3% at weeks 0–88; 16–22.5% at 72 weeks [5]; 15.7% at 72 weeks in T2D
Adverse events	Gastrointestinal: 77% [9]–91% [4]	Gastrointestinal: 52.0% [9]	Gastrointestinal: 16.3%–35.5% [15]

Abbreviations: GLP-1R: glucagon-like peptide-1 receptor; GCGR: glucagon receptor; HbA1c: glycated hemoglobin.

further affect these outcomes.[18] Therefore, the reported weight loss effects of survodutide may be inflated in trials where a substantial majority of participants are women, such as the obesity trial where 68% of subjects were women.[4]

Thirdly, while direct comparisons are lacking, survodutide appears less effective than retatrutide, a tri-agonist targeting GLP-1R, GCGR, and GIP receptors.[16] In a phase 2 obesity trial with a more balanced gender distribution (48% women), retatrutide achieved a placebo-corrected weight reduction of approximately 22% after 48 weeks.[16] Lastly, the majority of subjects (78–83%) evaluated with survodutide were of White ethnicity, which may limit generalizability to other racial or ethnic groups.[4,9]

2.6. Future directions

Ongoing phase 3 trials, such as SYNCHRONIZE-CVOT, aim to elucidate its long-term efficacy and safety. These trials incorporate slower dose titration strategies to mitigate gastrointestinal issues. Furthermore, survodutide is under investigation for its potential benefits in treating non-alcoholic steatohepatitis (NASH), with its impact on mortality and cardiovascular events also being assessed in the SYNCHRONIZE-CVOT trial.[19] The development of other dual GLP-1R and GCGR agonists, including pemvidutide and mazdutide, underscores ongoing efforts to optimize therapeutic options for obesity, type 2 diabetes, and NASH.[20]

3. Conclusion

Survodutide, a dual GLP-1 and GCGR agonist, has shown promise in phase 2 trials for type 2 diabetes and obesity, demonstrating significant reductions in weight and HbA1c levels over 46 weeks. However, persistent concerns regarding increased gastrointestinal side effects remain. However, ongoing research will refine the therapeutic role of survodutide and contribute to the development of novel dual agonists aimed at enhancing safety and effectiveness profiles.

4. Source of Funding

None.

5. Conflict of Interest

None.

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Author biography

Abdelmoneim B. Yousif, Pharmacist https://orcid.org/0009-0006-4940-9968

Ebtihal Abdelmoneim Hassan, Consultant

Mohamed Fawzi Mudarres, Nephrology Fellow

Musaab Fahmi Yousef, Medical Student

Abdelmonem Badawi, -

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