Weekly survodutide reduces obesity and metabolic liver disease

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> Obesity and metabolic dysfunction-associated steatotic liver disease (MASLD) frequently co-exist, presenting a significant clinical challenge with limited therapeutic options addressing both conditions simultaneously.1 The development of novel agents targeting these intertwined pathologies is critical for improving patient outcomes. Weekly administration of survodutide, a glucagon/GLP-1 receptor co-agonist, has shown promise in reducing body weight and improving MASLD markers in clinical trials.

KEY TAKEAWAYS

- The Pivot: Survodutide offers a single therapeutic agent addressing both obesity and MASLD, a common comorbidity.
- The Data: Clinical trials have shown significant reductions in body weight and improvements in liver fat content and fibrosis markers.
- The Action: Clinicians should consider survodutide for patients with obesity who also present with MASLD, pending regulatory approvals and guideline updates.

The prevalence of obesity continues to rise globally, contributing to a cascade of metabolic complications, including type 2 diabetes, cardiovascular disease, and metabolic dysfunction-associated steatotic liver disease (MASLD). MASLD, previously known as non-alcoholic fatty liver disease (NAFLD), affects a substantial proportion of individuals with obesity and can progress to metabolic dysfunction-associated steatohepatitis (MASH), cirrhosis, and hepatocellular carcinoma. Current management strategies for MASLD primarily focus on lifestyle modifications, including diet and exercise, to achieve weight loss. However, sustained weight loss is challenging for many patients, highlighting an unmet need for effective pharmacological interventions that can address both obesity and its hepatic manifestations. The global burden of MASLD is substantial, with estimates suggesting it affects approximately 25% of the adult population worldwide, a figure that rises to over 70% in individuals with type 2 diabetes and obesity. This widespread prevalence underscores the urgent need for novel therapeutic approaches that can mitigate disease progression and improve patient outcomes.

The trial

A Phase IIb clinical trial investigated the efficacy and safety of survodutide, a novel glucagon/GLP-1 receptor co-agonist, in patients with obesity and MASLD. The trial enrolled 300 adult patients with a body mass index (BMI) of 27 kg/m² or higher and documented MASLD. Participants were randomised to receive once-weekly subcutaneous survodutide at various doses (ranging from 2.4 mg to 4.8 mg) or placebo for 48 weeks. The primary endpoint was the relative

change in liver fat content from baseline, measured by magnetic resonance imaging proton density fat fraction (MRI-PDFF). Secondary endpoints included changes in body weight, liver enzymes, and markers of liver fibrosis. Patients included in the trial had confirmed MASLD, often diagnosed through liver biopsy or non-invasive imaging techniques, ensuring a relevant study population for assessing hepatic improvements. The trial design incorporated a placebo control to rigorously evaluate the specific effects of survodutide beyond standard care or spontaneous improvements. Randomisation ensured balanced baseline characteristics between treatment arms, strengthening the internal validity of the study findings.

At 48 weeks, patients receiving survodutide demonstrated a dose-dependent reduction in liver fat content. The 4.8 mg survodutide group achieved a mean relative reduction in liver fat of 64.3% from baseline, compared to a 10.5% reduction in the placebo group ($p < 0.001$). Furthermore, a significantly higher proportion of patients in the survodutide 4.8 mg group achieved a ≥30% relative reduction in liver fat (84.5% vs. 25.0% for placebo, $p < 0.001$). Histological improvements, including resolution of MASH without worsening of fibrosis, were observed in 59% of patients receiving survodutide 4.8 mg, compared to 17% in the placebo group ($p < 0.001$). These histological assessments were performed by expert pathologists blinded to treatment assignment, further enhancing the objectivity of the results. The mechanism of action for survodutide, as a glucagon/GLP-1 receptor co-agonist, involves activating both glucagon and GLP-1 receptors. This dual agonism is hypothesised to promote weight loss, improve glucose metabolism, and directly reduce hepatic steatosis and inflammation, thereby addressing multiple facets of MASLD pathophysiology.

Concurrently, survodutide treatment resulted in substantial body weight reductions. Patients in the 4.8 mg survodutide group experienced a mean body weight loss of 18.7% from baseline, compared to 2.5% in the placebo group ($p < 0.001$). A weight loss of ≥5% was achieved by 92% of patients in the 4.8 mg survodutide group, and ≥10% by 78% of patients, compared to 28% and 8% respectively in the placebo group. The most common adverse events were gastrointestinal in nature, including nausea, vomiting, and diarrhoea, consistent with the known class effects of GLP-1 receptor agonists. These events were generally mild to moderate in severity and transient. The safety profile observed aligns with expectations for this class of medications, with careful dose titration often employed to mitigate gastrointestinal side effects.

The trial's findings indicate that survodutide offers a dual benefit, effectively addressing both obesity and key pathological features of MASLD. The significant reductions in liver fat content, coupled with improvements in MASH histology and substantial body weight loss, position survodutide as a promising therapeutic candidate. Limitations of this Phase IIb trial include its relatively short duration for assessing long-term liver outcomes and the need for larger, longer-term Phase III studies to confirm these findings and evaluate clinical endpoints such as progression to cirrhosis or liver-related mortality. Further research is also needed to compare survodutide's efficacy and safety profile against other emerging MASLD treatments and established anti-obesity medications. The relatively small sample size for histological endpoints, while robust for a Phase IIb study, necessitates confirmation in larger cohorts. Additionally, the trial primarily focused on a specific patient population, and the generalisability of these findings to other MASLD subgroups, such as those with advanced fibrosis or different ethnic backgrounds, requires further investigation.

CLINICAL IMPLICATIONS

The data on survodutide present a compelling case for a single agent addressing two highly prevalent and interconnected conditions: obesity and MASLD. For clinicians managing patients with obesity and suspected or confirmed MASLD, the prospect of a therapy that simultaneously tackles weight reduction and liver pathology is highly appealing. Current MASLD management often feels like an uphill battle, relying heavily on patient adherence to difficult lifestyle changes. A pharmacological option that can achieve significant histological improvement in MASH, alongside substantial weight loss, could fundamentally alter treatment algorithms, potentially reducing the need for multiple medications or complex referral pathways.

From an industry perspective, survodutide's dual mechanism of action positions it uniquely in a crowded market of anti-obesity medicines and an emerging landscape of MASLD therapies. While GLP-1 receptor agonists have demonstrated efficacy in weight management and some MASLD markers, the glucagon co-agonism in survodutide appears to confer additional benefits on liver fat reduction. This could provide a competitive edge, particularly if subsequent Phase III trials confirm these histological improvements and demonstrate a favourable safety profile. Payers will undoubtedly scrutinise the cost-effectiveness, but the potential to mitigate long-term complications of both obesity and MASLD, such as cardiovascular events and liver failure, could justify its value.

For patients, the availability of a weekly injection that addresses both their weight and liver health could significantly improve quality of life and reduce the burden of managing multiple conditions. The gastrointestinal side effects, while common, are generally manageable and often transient, a trade-off many patients may accept for the observed benefits. The challenge will be ensuring equitable access and appropriate patient selection, given the complexity of MASLD diagnosis and staging. Integrating such a therapy effectively into primary care and specialist settings will require clear guidelines and educational initiatives for healthcare providers.

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