

Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Survodutide

Evidence Summary

Survodutide is a dual GLP-1/GCG RA in development for overweight or obesity and MASH. There is a theoretical basis for neuroprotection, especially in patients with metabolic disease.

Neuroprotective Benefit: While there is early evidence that mono GLP-1 RAs may reduce incidence of dementia or mitigate decline and it is possible that survodutide could have similar effects, no preclinical or clinical work has tested this for survodutide.

Aging and related health concerns: Clinical trials suggest that survodutide has significant benefits for MASLD, MASH, and obesity. It is not known whether survodutide has benefit for individuals without metabolic dysfunction.

Safety: Survodutide frequently causes gastrointestinal events, and there were high levels of treatment discontinuation due to adverse events. Larger trials may be needed to identify any rare but serious adverse events.

Availability: In clinical development	Dose: Dosing and dose escalation is still being tested. Survodutide is administered via once-weekly subcutaneous injection. Doses of 0.3 mg to 6 mg have been tested in trials.	Sequence: HAc4cQGTFTSDYSKYLDE RAAKDFIK*WLESA Survodutide is a 29-amino-acid peptide (Zimmermann et al., 2022).
Half-life: 6 days	BBB: Not yet reported. See information in the 'Neuroprotection' section.	
Clinical trials: The largest meta-analysis of survodutide included 1,272 people; two additional phase 3 trials with a combined total of 941 participants were published in June 2026.	Observational studies: There are no observational studies of survodutide.	

What is it?

Survodutide (BI 456906) is a 29 amino acid long peptide that agonizes both the glucagon (GCG) receptor and the glucagon-like peptide-1 (GLP-1) receptor; survodutide is derived from the gut peptide oxyntomodulin that activates both receptors ([Zimmermann et al., 2022](#)). There are several approved GLP-1 receptor agonists (GLP-1 RAs), one approved dual GIP/GLP-1 receptor agonist (dual GIP/GLP-1 RA), and one triple GLP-1/GIP/GCG agonist in late-stage development. Detailed reports on these two classes of drugs can be found on the [CognitiveVitality Reports](#) page. Both mono and dual agonists have been approved for use in type 2 diabetes as well as for overweight and obesity, and one GLP-1 RA called semaglutide has been approved for treatment of metabolic dysfunction-associated steatohepatitis (MASH). Several trials are exploring other indications for mono, dual, and triple agonists, including metabolic dysfunction-associated steatotic liver disease (MASLD).

GLP-1 is an incretin, which are peptide hormones that stimulate insulin secretion. The native peptides have short half-lives and are rapidly degraded by an enzyme known as dipeptidyl peptidase-4 (DPP4). The mono, dual, and triple agonists that are either in development or on the market have all been



modified to resist degradation and have longer half-lives than the native peptide. GLP-1 and its analogs stimulate insulin production, slow gastric emptying, and inhibit glucagon release in normo- and hyperglycemic states ([Müller et al., 2019](#)). Glucagon is a peptide hormone that is produced by pancreatic alpha cells. Glucagon is known to increase hepatic glucose output between meals, as well as enhance hepatic fatty acid oxidation and lipolysis, modulate amino acid metabolism between meals, and may reduce food intake and increase energy expenditure. Dysregulation of glucagon is thought to play a role in metabolic disorders like type 2 diabetes ([Rix et al., 2019](#); [Urva et al., 2022](#)). The simultaneous agonism of both GLP-1 and GCG receptors thus increases energy expenditure while decreasing energy intake, as demonstrated by the peptide oxyntomodulin which agonizes both receptors ([Zimmermann et al., 2022](#)), offering an attractive therapeutic strategy for treatment of obesity and related conditions.

Agonizing different receptor(s) can lead to different clinical effects as can the relative ratio of receptor agonism activity ([Thomas et al., 2024](#); [Long et al., 2026](#)). Survodutide has an eight-fold greater activation of GLP-1 receptors than glucagon receptors, a necessary balance to provide benefits without leading to adverse glycemic events ([Kaplan et al., 2026](#)).

Survodutide is under development for overweight or obesity and MASH. Phase 3 trials have been completed in these populations. Ongoing studies are also exploring the effects in patients with MASH who have cirrhosis or liver fibrosis, in patients with chronic kidney disease, and on glycemic control in patients with type 2 diabetes ([clinicaltrials.gov](#)).

Neuroprotective Benefit: While there is early evidence that mono GLP-1 RAs may reduce incidence of dementia or mitigate decline and it is possible that survodutide could have similar effects, no preclinical or clinical work has tested this for survodutide.

Types of evidence:

- 1 meta-analysis or systematic review
- 5 clinical trials
- 6 observational studies
- 4 reviews
- Several laboratory studies



Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

No clinical or observational studies have assessed whether survodutide may prevent dementia or decline or improve cognitive function.

There is strengthening observational evidence ([Wium-Andersen et al., 2019](#); [Siddeeqe et al., 2024](#); [Tang et al., 2024](#); [Xie et al., 2025](#)) and post-hoc pooled data from randomized controlled trials ([Nørgaard et al., 2022](#); [Seminer et al., 2025](#)) that compared to other second-line diabetes treatments, GLP-1 RAs may be associated with lower incidence of dementia diagnosis in patients with metabolic diseases like type 2 diabetes. A target trial emulation also found that semaglutide, one GLP-1 RA, was associated with a lower incidence of dementia diagnosis compared to other antidiabetic medications (including other GLP-1 RAs) in patients with type 2 diabetes ([Wang et al., 2024](#)). Some very initial small studies in patients with obesity and either prediabetes or early type 2 diabetes found that treatment with GLP-1 RAs was associated with improvement in cognitive function compared to lifestyle counseling ([Vadini et al., 2020](#)).

If these observational and early clinical findings of the preventative potential of GLP-1 RAs are persistent and are further supported by findings in large clinical trials, survodutide may theoretically have similar effects if the effects are related to GLP-1 receptor agonism. It is also possible that survodutide could have separate effects through GCG receptor agonism, or through an interaction of the two receptor agonism effects. Studies specific to survodutide as well as data from single GCG agonists, as well as mechanistic preclinical work, will be needed to assess whether these preliminary findings with GLP-1 RAs are relevant to related drug classes and are clinically relevant.

Human research to suggest benefits to patients with dementia:

No clinical or observational studies have tested the effects of survodutide in patients with dementia.

Related drugs like GLP-1 RAs have been explored for use in patients with dementia. After several small trials of different GLP-1 RAs in various neurodegenerative diseases, two large Phase 3 trials were initiated to test the effects of semaglutide in patients with MCI or early-stage AD. These trials, known as Evoke and Evoke+, enrolled a total of 3,808 patients and randomized them to receive either oral semaglutide or placebo one a day for 156 weeks. Participants receiving semaglutide started at a 3 mg

dose, titrated up to 7 mg at 4 weeks, and then up to 14 mg at 8 weeks. The primary outcome of the study was the change in CDR-SB at week 104.

There was no difference in cognitive function between the two groups at week 104 as measured by CDR-SB or any other tested measure (MoCA, ADAS-Cog-13, MMSE, ADCOMS). There was no trend towards benefit in daily function as measured by ADCS-ADL, or time to progression to dementia. The researchers also examined levels of several blood and CSF biomarkers, including p-tau181, p-tau217, eMBTR-tau243, A β 40 and A β 42, GFAP, neurofilament light, high-sensitivity C-reactive protein (hsCRP) levels, and other inflammatory markers. The study team found significant decreases in several relevant biomarkers in those treated with semaglutide compared to those who received placebo treatment. The researchers hypothesized that the shift in biomarkers was not of great enough magnitude to affect clinically meaningful change in cognition ([Cummings et al., 2026](#)). More information on these and other studies can be found in the GLP-1 RA report ([CognitiveVitality](#)).

These findings may or may not speak to the potential for treatment of survodutide. It is possible that survodutide would have the biggest impact as a prevention tool before any onset of cognitive symptoms rather than as a treatment for MCI or dementia, as may be the case for semaglutide and other GLP-1 RAs. It is also possible that the GCG agonism of survodutide could lead to different effects. Specific research on survodutide in these populations is needed to answer these questions.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Survodutide is under development for metabolic disorders such as MASLD/MASH and obesity, as discussed in depth in the 'Aging and related health conditions' section. The clinical data thus far suggest that survodutide can lead to improvements in body weight and body composition, and may improve glycemic indices, lipid profiles, and blood pressure control. As obesity and other metabolic parameters increase the risk of dementia ([Livingston et al., 2024](#)), treating these conditions may lead to a reduction in dementia as well.

It is theoretically possible that agonizing GLP-1 receptors can have direct neuroprotective effects, as these receptors are found in the brain. Glucagon receptors are also thought to be present in the brain, though there are conflicting results and the effects of glucagon agonism in the brain is less well understood than that of GLP-1 receptors ([Lasher et al., 2022](#)). Preclinical work suggests that stimulating GLP-1 receptors in the brain may protect against apoptosis, excitotoxicity, and oxidative stress, while

promoting neuronal growth, differentiation, autophagy, and synaptic plasticity. Animals that do not have GLP-1 receptors have memory formation deficits, whereas animals that overexpress this receptor in the hippocampus had improvements in learning and memory ([Ji et al., 2016](#); [Kopp et al., 2022](#); [Nowell et al., 2023](#); [Luna-Marco et al., 2023](#); [Kalinderi et al., 2024](#)).

Interestingly, a preclinical study compared the effects of a mono GLP-1 RA known as dulaglutide to a dual GLP-1/GCG RA called mazdutide in a mouse model of type 2 diabetes. The study found that compared to dulaglutide, mazdutide significantly improved cognitive performance and had greater protection against neuronal loss, though both drugs were protective compared to control mice ([Dong et al., 2025](#)). A preclinical study tested the effects of an oxyntomodulin analog, which is a peptide hormone that agonizes both GLP-1 and GCG receptors, in APP/PS1 mouse models of AD. They found that the oxyntomodulin analog mitigated memory impairments, reduced A β plaque load, and attenuated deficits in hippocampal long-term potentiation ([Wang et al., 2020](#)).

Whether these effects are a class effect and thus applicable to survodutide or if they are drug-specific is not yet known; no study was identified that tested the effects of survodutide on cognition in any model.

There are two other factors that may influence the mechanism of neuroprotection: the relative agonism of survodutide to its two receptor targets, and its capacity to cross the blood-brain barrier (BBB). The specific agonism action at each receptor may influence the clinical effects of any given drug, particularly in comparison with other drugs in the same class or related classes ([Thomas et al., 2024](#)). It is not yet known if or how this affects any neuroprotective effects, but it nonetheless may be a factor. Second, it is not known if survodutide crosses the BBB. There are mixed findings on the BBB permeability of incretin therapies, with some appearing to readily cross the BBB while others have limited penetrance ([Kopp et al., 2022](#)). Early preclinical data suggest that there is limited penetration of survodutide into the brain, though this requires confirmation in human studies ([Zimmermann et al., 2026](#)). It is also possible that survodutide and other related drugs do not need to cross the BBB to have an effect in the brain, as they can access and accumulate in parts of the brain that are not protected by the BBB. Additionally, as survodutide and related drugs affect levels of glucose, insulin, and other molecules that can cross the BBB, survodutide could affect brain health via modulating levels of those compounds.

APOE4 interactions:

It is not known whether there are differential effects of survodutide based on APOE4 carrier status.

Aging and related health concerns: Clinical trials suggest that survodutide has significant benefits for MASLD, MASH, and obesity. It is not known whether survodutide has benefit for individuals without metabolic dysfunction.

Types of evidence:

- 9 meta-analyses or systematic reviews
- 5 clinical trials
- 4 reviews
- 1 laboratory studies

MASLD/MASH: PROBABLE BENEFIT

SYNCHRONIZE-MASLD was a 48-week phase 3 RCT of survodutide in 216 adults with obesity and at-risk metabolic dysfunction-associated steatotic liver disease (MASLD), defined as MASLD with evidence of liver inflammation and/or fibrosis or biopsy-confirmed metabolic dysfunction-associated steatohepatitis (MASH). Participants were randomized to receive either survodutide or matching placebo in a once-weekly subcutaneous dose. Survodutide dosing started at 0.3 mg and was uptitrated over 24 weeks to the maximum dose of 6 mg, where dose was maintained until the end of the 48-week dosing period. All patients also received nutritional and physical activity counseling. The study met its co-primary endpoints including a significant difference between groups of a $\geq 30\%$ reduction in liver fat content as assessed by MRI. In the survodutide group, 84.2% of the patients had a $\geq 30\%$ reduction in liver fat content compared to 24.3% of the placebo group ($p < 0.0001$). In the survodutide group, 61% of patients reached $< 5\%$ liver fat content at 48 weeks compared to 5.7% of the placebo group. Survodutide treatment also resulted in significant improvements in indices of liver health and liver inflammation. There were a variety of other significant improvements in cardiometabolic parameters that are discussed in their respective sections ([Kaplan et al., 2026](#)).

Data from [le Roux et al., 2026](#), discussed below, and from [Noureddin et al., 2026](#) which describes a mediation analysis of a phase 2 trial of survodutide for MASH, suggest that the improvements on liver indices such as improvement of fibrosis without worsening of MASH or resolution or improvement of MASH without worsening of fibrosis are not due entirely to weight reduction. This suggests a direct impact of survodutide on hepatic health.

Some meta-analyses and systematic reviews have assessed survodutide for MASLD/MASH. It should be noted that these analyses were published before the phase 3 SYNCHRONIZE trials and thus only include earlier trials published before summer 2026; these meta-analyses are described in brief below.

[Sun et al., 2026](#) performed a systematic review and network meta-analysis of pharmacotherapies for improvement of liver fibrosis in patients with MASLD and early fibrosis. They included 13 total RCTs, one of which tested survodutide. They found that compared to placebo, 6 mg weekly survodutide was significantly more effective at achieving MASH resolution without worsening fibrosis (RR=7.25; 95% CI 2.07 to 25.36) and had the best efficacy as per SUCRA analysis (92%). The network analysis by [Banerjee et al., 2026](#) that assessed anti-diabetic agents for MASH without cirrhosis similarly found that survodutide improved fibrosis compared to placebo and reported that survodutide had the highest ranking (SUCRA=0.822 to 0.849) for MASH resolution in their analysis. [Souza et al., 2025](#) performed a systematic review and network meta-analysis comparing pharmaceutical treatments for biopsy-confirmed MASH and reported that compared to placebo, survodutide improved fibrosis without worsening MASH. Survodutide was one of the top three interventions for achieving MASH resolution without worsening fibrosis in their analysis (SUCRA=90.87)

Neither of these network meta-analyses included retatrutide, a triple GLP-1/GIP/GCG agonist; other meta-analyses, like that from [Wang et al., 2025](#), instead find that retatrutide has the most obvious treatment benefits. Further work, including head-to-head studies, are needed to clarify relative efficacy.

Overweight or Obesity: PROBABLE BENEFIT

SYNCHRONIZE-1, detailed in [le Roux et al., 2026](#), was a 76-week phase 3 RCT of survodutide compared to placebo in 725 patients with obesity or overweight with at least one obesity-related complication. Participants were randomized to receive up to 3.6 mg of survodutide, up to 6 mg of survodutide, or placebo via once-weekly subcutaneous injection using a dose escalation scheme. All patients were also encouraged to follow a reduced-calorie diet and engage in physical activity. The trial met its two primary endpoints, which were percent change in body weight and reduction in body weight of at least 5% from baseline to week 76, shown in the table below as treatment-regimen estimands. Secondary endpoints included reduction in waist circumference and the percent of participants who had weight reductions of $\geq 10\%$, $\geq 15\%$, and $\geq 20\%$, and are also included in the table below.

	Placebo	3.6 mg survodutide	6 mg survodutide
Mean percent change in body weight	-5.4%	-12.2% (p<0.001)	-13% (p<0.001)
≥5% body weight reduction	46.3%	72.6% (p<0.001)	71.9% (p<0.001)
≥10% body weight reduction	26%	55.2% (p<0.001)	56.6% (p<0.001)
≥15% body weight reduction	12%	35.7% (p<0.001)	45.9% (p<0.001)
≥20% body weight reduction	6.6%	24.9% (p<0.001)	28% (p<0.001)
Change in waist circumference (cm)	-5.4	-10.5 (p<0.001)	-11.5 (p<0.001)

Importantly, a subgroup of participants (n=25 per group) underwent MRI imaging, and a prespecified analysis assessed the relative body composition from baseline to end of trial. The authors note that the higher dose of survodutide had numerically great decrease in liver fat content compared to the lower dose of survodutide, despite having similar reductions in total body fat. They speculate that this may indicate that survodutide has particular benefits for body composition outside of general impact on body weight.

	Total Body Fat	Visceral Fat	Liver Fat	Lean Body Volume
Placebo	-9.5%%	-11.8%	-24.5%	-2.9%
3.6 mg survodutide	-22.9%	-29.8%	-46%	-7.2
6 mg survodutide	-27.8%	-34%	-63.1%	-9.8%

A review article notes that the reduction in visceral and liver fat tissue was greater than what would be expected from overall weight reduction seen in these trials, and that the reduction could have specific healthspan benefits ([Bijoch, 2026](#)).

SYNCHRONIZE-MASLD was a 48-week phase 3 RCT of survodutide in 216 adults with obesity and at-risk metabolic dysfunction-associated steatotic liver disease (MASLD) or biopsy-confirmed metabolic

dysfunction-associated steatohepatitis (MASH). The trial met its co-primary endpoint of a significant difference between groups in percentage of bodyweight change from baseline to end of the 48-week dosing. In the survodutide group, patients had an average bodyweight change of -12.2% compared to -1% in the placebo group ($p < 0.0001$). In patients with type 2 diabetes (T2D), there was an average of -9.9% change in body weight in the survodutide group compared to -2.0% in the placebo group. Survodutide participants also had a mean change of -11.1 cm in waist circumference compared to -1.9 cm in the placebo group ($p < 0.0001$) ([Kaplan et al., 2026](#)).

A prespecified subgroup analysis was performed for a phase 2 trial; this trial included 387 people with overweight or obesity and tested doses of survodutide ranging from 0.5 mg to 4.8 mg or matching placebo once weekly for 46 weeks. The subgroup analysis found that women had greater reductions in weight and waist circumference than men, and that participants with lower baseline BMI had greater proportional reductions in bodyweight than those with higher baseline BMI ([Je Roux et al., 2025](#)).

Systematic reviews and meta-analyses published before the announcement of the phase 3 trials above come to similar findings of the efficacy of survodutide.

[Abulehia et al., 2026](#) reports on a network meta-analysis and comparative effectiveness study of investigational glucagon receptor agonists, including survodutide, in patients with obesity, overweight, or type 2 diabetes. They found that compared to placebo, use of retatrutide led to the greatest weight reduction, followed by survodutide (MD=-10.74 kg; 95% CI -15.68 to -5.80).

[Xiao et al., 2025](#) reports on a systematic review and meta-analysis of survodutide in 6 trials with a total of 1,272 participants. They found that compared to placebo, survodutide significantly decreased body weight (WMD= -6.7 kg; 95% CI -10.0 to -3.4, $p < 0.001$) and waist circumference; they found that these effects were greater at doses higher than 2.4 mg and with treatment durations of greater than 16 weeks.

[Awad et al., 2025](#) performed a meta-analysis of RCTs of survodutide for obesity. They included 4 trials comprising a total of 980 people, using doses ranging from 0.3 mg to 4.8 mg survodutide or matching placebo once or twice weekly. Compared to placebo, survodutide treatment led to significant reductions in body weight (SMD: -1.5; 95% CI -2.05 to -0.95, $p < 0.00001$), as well as significant reductions in waist circumference and significantly more people with reductions of $\geq 5\%$ and $\geq 10\%$ of bodyweight.

Meta-analyses by [Dutta et al., 2025](#) and [Wan et al., 2024](#) include approximately 1,000 participants each and both similarly find that survodutide treatment leads to significant reductions in weight compared to placebo.

Cardiovascular Disease: POSSIBLE BENEFIT

The impact of survodutide on cardiovascular health is being assessed in an ongoing phase 3 trial known as SYNCHRONIZE-CVOT ([NCT06077864](#)).

SYNCHRONIZE-MASLD tested survodutide in 216 participants and reported that compared to placebo, patients who received survodutide had significant reductions in systolic blood pressure (-7.4 mmHg; $p=0.0003$) and diastolic blood pressure (-2.7 mmHg; $p=0.0478$). They also reported benefits in lipid profiles and high sensitivity CRP (hsCRP) with survodutide treatment, summarized in the table below as relative percent change from baseline ([Kaplan et al., 2026](#)).

	Placebo	Survodutide (6 mg)	P Value
Triglycerides	0.7	-30.3	<0.0001
Total cholesterol	-1.8	-10.5	0.0039
LDL-c	-2.4	-10.8	0.0834
HDL-c	1.4	5.0	0.1834
VLDL cholesterol	-0.6	-32.8	<0.0001
hsCRP	-7.2	-46.2	0.0003

SYNCHRONIZE-1 assessed the effects of up to 3.6 mg or up to 6 mg survodutide compared to placebo in 725 participants with overweight or obesity. In this population, there was no significant improvement in systolic or diastolic blood pressure in either survodutide group compared to placebo. There were numerical improvements in some lipid parameters such as levels of triglycerides and VLDL-cholesterol in the survodutide group compared to the placebo group ([le Roux et al., 2026](#)).

[Xiao et al., 2025](#) reports on a systematic review and meta-analysis of survodutide in 6 trials with a total of 1,272 participants; this analysis does not include the phase 3 results above. They reported that there were modest but statistically significant reductions in total cholesterol, triglycerides, and blood pressure.

Diabetes: POSSIBLE MODEST BENEFIT

SYNCHRONIZE-MALSD recruited patients with obesity and MASLD or MASH. They reported that participants receiving survodutide had significant improvements in HbA_{1c} as detailed in the table below as absolute percent change.

	Placebo	Survodutide	P Value
Overall	-0.02%	-0.6%	<0.0001
With T2D	0.2%	-0.6%	<0.0001
Without T2D	-0.1%	-0.6%	0.0019

SYNCHRONIZE-1 included patients with obesity or overweight and an obesity-related complication and excluded diabetes. They reported numerical improvements in HbA_{1c}, fasting plasma glucose, and fasting plasma insulin in both survodutide groups compared to placebo ([le Roux et al., 2026](#)).

[Xiao et al., 2025](#) details a systematic review and meta-analysis of survodutide in 6 trials with a total of 1,272 participants. They found that survodutide significantly reduced HbA_{1c} compared to placebo (WMD=-0.66%; 95% CI -1.08 to -0.23, p=0.002), but with significant heterogeneity. They noted that these HbA_{1c} reductions are relatively modest compared to other dual and triple agonists like tirzepatide and retatrutide.

[Awad et al., 2025](#) performed a meta-analysis of RCTs of survodutide. They included 4 trials comprising a total of 980 people, using doses ranging from 0.3 mg to 4.8 mg survodutide or matching placebo once or twice weekly. They reported that treatment with survodutide led to significant reduction in HbA_{1c} compared to placebo (MD=-1.12; 95% CI -1.33 to -0.9; p<0.00001). This meta-analysis did not include the above phase 3 trials. Other meta-analyses, such as a network meta-analysis by [Abulehia et al., 2026](#) of all investigational glucagon receptor agonists, did not find that survodutide had a statistically significant impact on HbA_{1c}.

Safety: Survodutide frequently causes gastrointestinal events, and there were high levels of treatment discontinuation due to adverse events. Larger trials may be needed to identify any rare but serious adverse events.

Types of evidence:

- 2 meta-analyses or systematic reviews
- 2 clinical trials
- 1 review
- 1 news article
- 2 laboratory studies

Like other incretins therapies, the most common adverse events for survodutide are gastrointestinal in nature, including nausea, vomiting, diarrhea, and constipation. However, the evidence thus far suggests that these events occur more frequently with survodutide than the approved mono and dual agonists, as well as the investigational triple agonist retatrutide, in the clinical trials to date.

SYNCHRONIZE-1 was a 76-week phase 3 RCT of survodutide compared to placebo in 725 patients with obesity or overweight with at least one obesity-related complication. Participants were randomized to receive up to 3.6 mg of survodutide, up to 6 mg of survodutide, or placebo via once-weekly subcutaneous injection using a dose escalation scheme. All patients were also encouraged to follow a reduced-calorie diet and engage in physical activity. There were no deaths or cases of pancreatic cancer, thyroid cancer, or acute pancreatitis. There was one adjudicated major adverse cardiovascular event of ischemic stroke in the placebo group. One participant in the low dose survodutide group reported an attempted suicide in the context of psychosocial stressors; depression was reported more commonly in the placebo group than in the survodutide groups. As with other incretin drugs, there was an increase in heart rate of 3.2 to 3.5 beats per minute in the survodutide group compared to the placebo group, which had a mean change of -0.4 beats per minute; there was a high rate of treatment discontinuation in this trial; at the end of the trial, 59.9%, 64.7%, and 65.7% of participants were still receiving their assigned placebo, low dose survodutide, and high dose survodutide treatment, respectively. Other obesity medications including GLP-1 RAs were prohibited, but at the end of the trial 16.5%, 2.5%, and 3.7% of the placebo, low dose survodutide, and high dose survodutide treatment, respectively, reported taking a non-survodutide GLP-1 RA. The table below summarizes key safety data as percent of participants ([le Roux et al., 2026](#)).

	Placebo	3.6 mg survodutide	6 mg survodutide
Any adverse event	86%	96.3%	97.5%
Serious adverse event	6.2%	8.3%	8.3%
Trial discontinuation for AE	0.8%	2.5%	1.7%

Treatment discontinuation for AE	5.4%	23.7%	24.8%
Treatment discontinuation for GI AE	2.9%	17.8%	20.2%
Nausea	17.4%	61%	64.9%
Vomiting	6.2%	40.7%	44.6%
Diarrhea	18.6%	32%	39.7%
Constipation	12.4%	31.1%	32.6%
GI disorder	47.9%	80.9%	89.7%
Asymptomatic pancreatic hyperenzymemia	1.2%	2.5%	1.7%

SYNCHRONIZE-MASLD was a 48-week phase 3 RCT of survodutide in 216 adults with obesity and at-risk metabolic dysfunction-associated steatotic liver disease (MASLD) or biopsy-confirmed metabolic dysfunction-associated steatohepatitis (MASH). Participants were randomized to receive either survodutide or matching placebo in a once-weekly subcutaneous dose. Survodutide dosing started at 0.3 mg and was uptitrated over 24 weeks to the maximum dose of 6 mg, where dose was maintained until the end of the 48-week dosing period. Overall, there was a similar rate of adverse events (87% vs. 78.6%) and serious adverse events (9.6% vs. 11.4%) in the survodutide vs. placebo group, respectively. Nausea (56.2%), vomiting (42.5%), diarrhea (29.5%), and constipation (28.1%) were common in the survodutide group, while none of these events were reported by more than 14.3% of placebo group participants. Many of the gastrointestinal events occurred during dose escalation and were mild to moderate in intensity. There was a higher incidence of hypo- and hyperglycemia in the placebo group than in the survodutide group. There were no adjudication-confirmed cases of drug-induced liver injury, acute pancreatitis, pancreatic cancer, or thyroid cancer. There was a greater increase in heart rate in the survodutide group (3.6 beats per minute) compared to placebo (0.8 beats per minute). There were 2 cases of diabetic retinopathy in the survodutide group compared to no cases in the placebo group. There was one death in the placebo group; there were no details on the cause of death ([Kaplan et al., 2026](#)).

This trial had a high rate of treatment discontinuation, with 41.1% of the survodutide and 40% of the placebo group discontinuing treatment. In total, 23.3% of participants in the survodutide group discontinued treatment due to adverse events compared to 10% in placebo; 19.9% of survodutide patients discontinued due to gastrointestinal events compared to 4.3% of placebo. The authors

speculated that their protocol, which was originally relatively inflexible to dose escalation, may have contributed to issues with patient treatment tolerance ([Kaplan et al., 2026](#)).

While head-to-head trials are necessary to directly compare, the rates of treatment discontinuation due to adverse events in these SYNCHRONIZE trials appear to be higher than in phase 3 trials of semaglutide and tirzepatide ([StatNews](#)). However, it may be challenging to untangle how much treatment discontinuation is solely due to intolerability and how much is due to the availability of other mono and dual agonists that participants may prefer. It is also not yet known whether different dose escalation schemes can ease some of the tolerability issues.

The safety profile of survodutide has been assessed in meta-analyses, though these do not include the above phase 3 trial results.

[Xiao et al., 2025](#) details a systematic review and meta-analysis of survodutide in 6 trials with a total of 1,272 participants. They found that there was no significant difference in serious adverse events, but there was a significant increase in risk of treatment discontinuation due to adverse event (RR=4.07; 95% CI 2.18 to 7.6, $p<0.001$), and that this risk was higher in the first 16 weeks of treatment, and at doses higher than 2.4 mg. Survodutide treatment increased the risk of discontinuation due to GI adverse events (RR=7.07; 95% CI 2.61 to 19.14, $p<0.001$). Compared to placebo, survodutide significantly increased the risk of vomiting (RR=7.2; 95% CI 3.9 to 13.32), nausea (RR=3.08; 95% CI 2.34 to 4.06), diarrhea (RR=1.93; 95% CI 1.43 to 2.61), and dyspepsia (RR=3.54; 95% CI 1.90 to 6.60), all $p<0.001$. They reported that 71.2% of the discontinuation events in their analysis were due to gastrointestinal events, and that the risk of vomiting in particular was higher than analyses suggested for other incretin therapies.

[Awad et al., 2025](#) performed a meta-analysis of RCTs of survodutide. They included 4 trials comprising a total of 980 people, using doses ranging from 0.3 mg to 4.8 mg survodutide or matching placebo once or twice weekly. Their analysis indicated that the overall frequency of adverse events was not significantly different between the survodutide and placebo group. However, survodutide treatment had a higher risk of treatment discontinuation due to adverse events (RR=4.53; 95% CI 2.15 to 9.54; $p<0.00001$), vomiting (RR=6.64; 95% CI 3 to 14.7), nausea (RR=3.3; 95% CI 2.23 to 4.88) and diarrhea (RR=1.89; 95% CI 1.2 to 2.97), all $p<0.00001$. There was also an increased risk of dyspepsia.

Drug interactions:

The drug interactions of survodutide are not yet fully known. Given the partly overlapping agonism, survodutide may share at least some drug interactions in common with GLP-1 RAs and/or dual GIP/GLP-1 RAs, which have similar drug interaction profiles.

The in-depth drug interaction information can be seen in their respective reports on [Cognitive Vitality](#). In brief, both drug classes are known to have major interactions with bexarotene, as there is an increased risk of pancreatitis, and gatifloxacin and capivasertib, as there is an increased risk of hypo- or hyperglycemia. Mono and dual agonists may be contraindicated during surgery due to slowing of gastric emptying; this may also apply to survodutide and other similar drugs. There are also disease interactions with specific types of cancer, pancreatitis, and existing severe gastrointestinal disease. Patients with renal dysfunction and severe gastrointestinal events, as well as patients with diabetic retinopathy, may require additional monitoring. More research is needed to know whether these drug interactions do indeed apply to survodutide as well, and whether there are additional interactions or other nuances specific to dual GLP-1/GCG receptor agonism.

Research underway:

There are 8 trials investigating survodutide that are registered on [clinicaltrials.gov](#). The trials are all exploring the use of survodutide for metabolic syndromes such as type 2 diabetes, MASLD/MASH, or overweight/obesity, or are studies of the pharmacodynamics and pharmacokinetics of survodutide. No study is assessing the effects of survodutide on cognition or for use in patients with dementia.

Search terms:

Pubmed, Google: survodutide, BI 456906

- Cognition, dementia, MASH, MASLD, obesity, APOE4

Websites visited for survodutide

- [Clinicaltrials.gov](#)
- [PubChem](#)
- [DrugBank.ca](#)
- [Cafepharma](#)



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