*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.*

# Retatrutide

**Evidence Summary**

Retatrutide is a triple GIP/GLP-1/GCG RA in development for T2D, obesity, and MASLD. 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 retatrutide could have similar effects, no preclinical or clinical work has tested this for retatrutide.

**Aging and related health concerns:** Clinical trials thus far indicate that retatrutide could have significant benefits for treating diabetes, obesity, and MASLD, and may benefit other conditions. It is not clear whether retatrutide benefits healthy individuals.

**Safety:** Retatrutide is associated with GI events. These events are common, though often mild. Rare but serious events including increased liver enzymes, cardiac arrhythmias, pancreatitis, and cholecystitis have been observed in some but not all trials.

| | |
|---|---|
| **Availability**: In clinical development | **Dose**: Dosing and dose escalation is still being tested; doses of 0.5 to 12 mg via once-weekly subcutaneous injections have been tested. |
| **Half-life**: 6 days | **BBB**: Not yet reported. See information in the 'Neuroprotection' section. |
| **Clinical trials**: A meta-analysis of three clinical trials included 640 patients | **Observational studies**: There are no observational studies of retatrutide. |

**What is it?**

Retatrutide (LY3437943) is a single peptide that can agonize the glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide 1 (GLP-1), and glucagon (GCG) receptors (Jastreboff et al., 2023). There are several approved GLP-1 receptor agonists (GLP-1 RAs) as well as one approved dual GIP/GLP-1 receptor agonist (dual GIP/GLP-1 RA). Detailed reports on these two classes of drugs can be found on the Cognitive Vitality Reports page. Both mono and dual agonists have been approved for use in type 2 diabetes as well as for overweight and obesity; several trials are exploring other indications, including metabolic dysfunction-associated steatotic liver disease (MASLD) / metabolic dysfunction-associated steatohepatitis (MASH).

GLP-1 and GIP are both incretins, 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. GIP and its analogs also stimulate insulin production and modulate glucagon release based on blood sugar levels. GIP and its analogs also increase the sensitivity of adipose tissue to insulin, as well as increase the lipid-buffering capacity of adipose tissue (Samms et al., 2020; Mishra et al., 2023). Dual agonism of GLP-1 and GIP receptors had clinically meaningful improvements in measures of glycemia, bodyweight, and cardiovascular risk factors like blood pressure and lipid profiles, and these improvements may be significantly greater than mono agonism of the GLP-1 receptor alone. Research has continued into other agonism combinations that may provide additional clinical benefit (Urva et al., 2022).

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). There has therefore been increasing interest in whether a triple agonism strategy may offer additional clinical benefits to mono or dual agonist approaches (Coskun et al., 2022; Urva et al., 2022). Besides for the specific receptors agonized, the relative ratio of receptor activity may influence the clinical effects (Rosenstock et al., 2023).

Retatrutide is under development for type 2 diabetes, overweight or obesity, and MASLD. Phase 3 trials are ongoing in these patient populations. Ongoing studies are also exploring the effects on cardiovascular events, renal outcomes, and osteoarthritis of the knee in patients with overweight or obesity (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 retatrutide could have similar effects, no preclinical or clinical work has tested this for retatrutide.

*Types of evidence:*

- 4 clinical trials
- 2 observational studies
- 7 reviews

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

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

There is preliminary observational evidence and post-hoc pooled data from randomized controlled trials that compared to other second-line diabetes treatments, GLP-1 RAs may be associated with a reduction in dementia diagnosis in patients with metabolic diseases like type 2 diabetes (Wium-Andersen et al., 2019; Nørgaard et al., 2022). 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 persist and are further supported by findings in large clinical trials, retatrutide may theoretically have similar effects if the effects are related to GLP-1 receptor agonism It is also possible that retatrutide could have separate effects through GIP or GCG receptor agonism, or through an interaction of some or all of the receptor agonism effects. Studies specific to retatrutide as well as data from dual 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 retatrutide in patients with dementia.

Related drugs like GLP-1 RAs have been explored for use in patients with dementia, but the studies have largely been small and have reported conflicting results (GLP-1 RA report).

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

Retatrutide is under development for metabolic disorders such as type 2 diabetes, obesity, and MASLD, which is discussed in depth in the 'Aging and related health conditions' section. The clinical data thus far suggest that retatrutide can lead to improvements in glycemic control and weight loss. As diabetes and obesity both independently increase the risk of dementia (Livingston et al., 2024), treating these conditions may lead to a reduction in dementia as well. Insulin resistance has also been observed in patients with dementia without metabolic syndrome(s); as dual GIP/GLP-1 RAs can improve insulin resistance, the drug class could exert a neuroprotective effect via improving insulin signaling (Girges et al., 2021).

It is possible that GLP-1 and GIP receptor agonism 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 or GIP 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. Preclinical studies of dual GIP/GLP-1 RAs report that the drugs can mitigate memory deficits or cognitive impairment in different animal models of AD. Some studies reported that dual GIP/GLP-1 receptors enhanced release of neurotrophic factors, improved mitochondrial health indices, or inhibited apoptosis, among other potentially neuroprotective roles. Both GLP-1 RAs and dual GIP/GLP-1 RAs have been reported to decrease aggregate burden in animal models of neurodegeneration, as well as reduce levels of inflammation (Ji et al., 2016; Maskery et al., 2020; Kopp et al., 2022; Nowell et al., 2023; Luna-Marco et al., 2023; Kalinderi et al., 2024).

There has not yet been any significant exploration of the effects of retatrutide in animal models of neurodegeneration or cognition. One preclinical paper tested the effects of a GLP-1 RA, dual GIP/GLP-1 RAs and retatrutide in cellular models. They found that mono, dual, and triple agonists all had neurotrophic and neuroprotective effects, as well as anti-inflammatory properties; retatrutide, along with the dual agonists, had enhanced benefits compared to the single GLP-1 RAs. There were hints at differences; for instance, only retatrutide significantly reduced caspase-3 activity (Kopp et al., 2024). Different triple agonists were found to have benefits in animal models of AD; the triple agonists appeared to improve spatial memory deficits and synaptic transmission, modulated apoptotic signaling, increased the levels of BDNF and neurogenesis, and reduced aggregate load, neuroinflammation, and oxidative stress (Tai et al., 2018; Li et al., 2018; Li et al., 2020). A triple agonist also mitigated memory and visual deficits in a model of traumatic brain injury (Li et al., 2020). These triple agonists were all synthesized peptides that were not given a name. Another triple agonist known as HM15211was reported to have benefits in an animal model of Parkinson's disease (PD), improving motor function and protecting dopaminergic neurons (Nowell et al., 2023). More work is needed to further explore these effects and to see whether retatrutide has similar effects.

There are two other factors that may influence the mechanism of neuroprotection: the relative agonism of retatrutide to its three 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. Retatrutide is less potent than endogenous glucagon or GLP-1, but much more potent than endogenous GIP (Coskun et al., 2022). It is not yet known if or how this affects any neuroprotective effects but may be a factor. Second, it is not known if retatrutide crosses the BBB. There are mixed findings on GLP-1 RAs and dual GIP/GLP-1 RAs, with some appearing to readily cross the BBB while others have limited penetrance (Kopp et al., 2022). It

is also possible that retatrutide 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 retatrutide and related drugs affect levels of glucose, insulin, and other molecules that can cross the BBB, retatrutide could affect brain health via modulating levels of those compounds.

***APOE4 interactions***:

It is not known whether retatrutide has differential effects based on APOE4 carrier status.

**Aging and related health concerns:** Clinical trials thus far indicate that retatrutide could have significant benefits for treating diabetes, obesity, and MASLD, and may benefit other conditions. It is not clear whether retatrutide benefits healthy individuals.

*Types of evidence:*

- 2 meta-analyses or systematic reviews
- 1 professional practice committee document
- 4 clinical trials
- 1 review
- 1 laboratory study

Retatrutide is being explored for use in type 2 diabetes, overweight and obesity, and metabolic dysfunction-associated steatohepatitis, among other potential uses. A meta-analysis of RCTs of retatrutide and the effect of retatrutide on weight and metabolic markers in patients with overweight, obesity, or type 2 diabetes found that retatrutide significantly reduces body weight, BMI, waist circumference, and increases the percentage of patients who achieve weight reduction of 5% or more (Pasqualotto et al., 2024). The included 3 studies are described in detail in their respective section.

**Overweight or Obesity:** PROBABLE BENEFIT

Jastreboff et al., 2023 details the results of a phase 2 trial of retatrutide in patients with obesity who did not have diabetes. The trial enrolled 338 patients who were randomized to either placebo or one of 6 retatrutide doses: 1 mg, 4 mg with an initial dose of 2 mg, 4 mg with an initial dose of 4 mg, 8 mg with an initial dose of 2 mg, 8 mg with an initial dose of 4 mg, or 12 mg with an initial dose of 2 mg. All dosing

was administered once weekly via subcutaneous injection. Dosing lasted for 48 weeks, and there was an additional 4-week safety follow up period. All patients also received lifestyle intervention, including regular dietary counseling sessions from a qualified professional. Below is the primary outcome: the least-squares mean percentage change in body weight at 24 weeks. The change at 48 weeks, a secondary outcome, is also below. For these analyses, the researchers combined the groups based on their final dose, regardless of initial dose.

| | **Placebo** | **1 mg** | **4 mg** | **8 mg** | **12 mg** |
|---|---|---|---|---|---|
| **24 weeks** | -1.6% | -7.2% | 12.9% | -17.3% | -17.5% |
| **48 weeks** | -2.1% | -8.7% | -17.1% | -22.8% | -24.2% |

Another outcome measure was the percent of people in each group who achieved 5%, 10%, or 15% weight reduction at 48 weeks of treatment based on the final dose, regardless of initial dose. The table below presents those results.

| | **Placebo** | **1 mg** | **4 mg** | **8 mg** | **12 mg** |
|---|---|---|---|---|---|
| **5%** | 27% | 64% | 92% | 100% | 100% |
| **10%** | 9% | 27% | 75% | 91% | 93% |
| **15%** | 2% | 16% | 60% | 75% | 83% |

There was also a greater reduction in waist circumference in all retatrutide groups as compared to placebo.

The authors assessed factors that might predict response in prespecified analyses. They found that patients with a starting BMI of 35 or higher and randomized to the 8 mg or 12 mg groups had a greater mean weight change than patients with starting BMIs less than 35 (26.5% and 26.4% vs. 21.3% and 21.5%, respectively). Women in these dose groups also had a higher mean weight change than men (28.5% and 26.6% vs. 19.8% and 21.9%). Post-hoc analyses of trials of GLP-1 receptors have also found more significant weight reductions in women than in men. Participants receiving retatrutide lost weight throughout treatment, and the weight-reduction curves indicated that a plateau had not yet been reached. The Phase 3 trial of retatrutide in patients with overweight or obesity will be longer.

There are indications that retatrutide might reduce weight for groups with other conditions or for otherwise healthy individuals. A 12-week study in 72 patients with type 2 diabetes also found significant

reductions in body weight in retatrutide patients compared to placebo (Urva et al., 2022). A single-ascending dose study in healthy participants also found a significant reduction in weight in the higher dose groups after a single dose compared to placebo; in the highest two dose groups, this weight reduction remained statistically significant out to 43 days after the single dose (Coskun et al., 2022).

While it is challenging to compare between studies, retatrutide has shown greater reductions in weight at maximum doses in comparison to other anti-obesity drugs in development and also approved drugs, including semaglutide and tirzepatide (Rosenstock et al., 2023; Kokkorakis et al., 2024; Peter Attia AMA 64).

**Diabetes:** PROBABLE BENEFIT

A Phase 1b and Phase 2 trial have evaluated retatrutide for use in patients with type 2 diabetes.

Rosenstock et al., 2023 reports on the results from a phase 2 trial of retatrutide in patients with type 2 diabetes who were treated with lifestyle changes and/or a stable dose of metformin. The trial randomized 281 participants to either placebo, an approved GLP-1 RA known as dulaglutide (1.5 mg), or retatrutide treatment for 36 weeks. The patients randomized to retatrutide were further randomized to 6 dosing groups: 0.5 mg, 4 mg (starting dose 2 mg), 4 mg (starting dose 4 mg), 8 mg (starting dose 2 mg), 8 mg (starting dose 4 mg), or 12 mg (starting dose 2 mg). The trial also tested different dose escalation protocols. Patients received their study medication via weekly subcutaneous injections. The primary outcome was the change in $HbA1_c$ at 24 weeks. At this timepoint, there were significant decreases in $HbA1_c$ from baseline in all retatrutide groups; these reductions were significantly greater than in placebo in all but the lowest retatrutide dose group (0.5 mg) (all $p<0.0001$). The reductions were also significantly more than the dulaglutide group in the 8 mg retatrutide (starting dose 2 mg) group ($p=0.0019$) and in the 12 mg retatrutide group ($p=0.0002$). These findings were similar at 36 weeks.

Significantly more patients in the 4, 8, and 12 mg retatrutide groups reached an $HbA1_c$ less than 7% or 6.5% than placebo. Significantly more patients in the 8 and 12 mg groups reached an $HbA1_c$ less than 5.7%, indicative of normoglycemia, than placebo, with numerically more patients in the 4 mg group achieving that target than placebo as well.

There were other benefits of retatrutide in this patient population; there were dose-dependent reductions in systolic and diastolic blood pressure as well as improvements in lipid profiles.

It should be noted that the dose of dulaglutide used is not the highest dose available, and only high dose dulaglutide is considered to have very high glycemic efficiency; lower doses are considered to have high glycemic efficiency. The higher doses were not available when the study was planned (ADA Standard of Care in Diabetes, 2024).

Urva et al., 2022 details the initial phase 1b study. The RCT enrolled and randomized 72 patients with type 2 diabetes; all participants were taking metformin before and throughout the study. Patients were allocated to one of three overall groups: placebo, dulaglutide (1.5 mg), or retatrutide. The retatrutide group was divided into five ascending dose cohorts. The first three retatrutide cohorts received either 1 mg, 1.5 mg, or 3 mg retatrutide for 12 weeks. The fourth cohort received 3 mg for the first four weeks, followed by 6 mg for the remaining 8 weeks. This cohort was called the 3/6 cohort. The final cohort received 3 mg for 2 weeks, then 6 mg for 2 weeks, then 9 mg for 4 weeks, and 12 mg for the last four weeks. This group was called the 3/6/9/12 group. All participants received their study drug as once weekly subcutaneous injections. The study ran between December 2019 and December 2020; the trial experienced significant discontinuation (28%) due to COVID-19.

The groups were small, and variable for some baseline parameters, including age, sex, and BMI. At the end of the trials, mean daily plasma glucose had significantly decreased in the 3 mg, 3/6 mg, and 3/6/9/12 mg groups compared to placebo. The $HbA1_c$ values also decreased in all active treatment groups, particularly in the 3 mg, 3/6 mg, and 3/6/9/12 mg groups.

Jastreboff et al., 2023 did not enroll patients with diabetes, but they did enroll patients with prediabetes. At the end of the dosing period, 72% of the patients who had received retatrutide and had prediabetes had reverted to normoglycemia (defined as an HbA1c of less than 5.7%); 22% of the placebo group had reverted to normoglycemia.

**Metabolic Dysfunction-Associated Steatotic Liver Disease (MALSD)**: POTENTIAL BENEFIT

The main study detailed in Jastreboff et al., 2023 had a substudy for patients with 10% or greater liver fat content as measured by MRI. This substudy was published by Sanyal et al., 2024. Patients were randomized to either placebo or 1 mg, 4 mg, 8 mg, or 12 mg retatrutide administered once weekly via subcutaneous injection; sample sizes for each group ranged from 18 to 22. Most of the change in liver fat occurred within the first 24 weeks of the trial. The relative liver fat reduction was significantly greater

in all dosing groups of retatrutide compared to placebo. The least-squares mean relative liver fat changes from baseline are detailed below:

| | Placebo | 1 mg | 4 mg | 8 mg | 12 mg |
|---|---|---|---|---|---|
| **24 weeks** | +0.3% | -42.9% | -57% | -81.4% | -82.4% |
| **48 weeks** | -4.6% | -51.3% | -59% | -81.7% | -86% |

Resolution of steatosis is defined as less than 5% total liver fat content. No patient in the placebo group reached this benchmark at either the 24- or 48-week timepoint; by comparison, 89% and 93% of patients in the 8 mg and 12 mg group had reached liver fat content of less than 5% at 48 weeks. While it is difficult to compare between studies, these treatment effects are some of the numerically largest reported thus far, including compared to GLP-1 RAs and dual GIP/GLP-1 RAs. It is thought that the glucagon receptor agonism may be providing additional liver fat reduction benefit.

Similar to the main study, participants in the retatrutide groups lost significantly more weight than the placebo group; waist circumference was also reduced. The reductions were comparable to the main study.

On a mechanistic level, as glucagon receptor activation may have more direct hepatic effects, it is possible that drugs that include glucagon receptor agonism will have more significant effects in MASLD/MASH populations than drugs that do not include glucagon receptor agonists, though this remains to be clinically explored and validated (Kokkorakis et al., 2024)

**Cardiovascular Outcomes**: POSSIBLE BENEFIT

Studies that focus on the effects of retatrutide on cardiovascular outcomes are ongoing. However, there are some initial data from published studies. Jastreboff et al., 2023, a study in patients with overweight or obesity, included some cardiovascular measures as exploratory outcomes. Compared to the placebo group, at the end of the 48-week dosing period patients who received doses of at least 4 mg retatrutide had greater reductions in systolic and diastolic blood pressure. The improvements were such that 41% of patients in the 8 mg retatrutide group and 30% of participants in the 12 mg group discontinued at least 1 anti-hypertensive medication. Heart rate did increase in these patients, as has been noted in trials of related drug classes; in this trial, there were dose-dependent increases in heart rate in the retatrutide groups up to 24 weeks. After 24 weeks, the heart rates declined, though they did not return

to baseline. The below table includes the reductions in blood pressure (in mmHg) from baseline at 36 weeks.

| | Placebo | 1 mg | 4 mg (2 mg start) | 4 mg (4 mg start) | 8 mg (2 mg start) | 8 mg (4 mg start) | 12 mg |
|---|---|---|---|---|---|---|---|
| **Systolic** | -2.9 (-5.4, -0.4) | -4.8 (-7.2, -2.3) | -8.7 (-12.7, -4.8) | -8.3 (-11.5, -5.1) | -8.8 (-11.6, -6.0) | -11.8 (-14.8, -8.8) | -8.8 (-11.9, -5.8) |
| **Diastolic** | -1.0 (-2.6, 0.5) | -2.2 (-4.0, -0.5) | -3.2 (-6.0, -0.4) | -2.9 (-5.0, -0.8) | -3.4 (-5.1, -1.7) | -3.5 (-5.6, -1.4) | -2.8 (-4.6, -0.9) |

Patients treated with retatrutide also had improvements in levels of triglycerides (trigly.), total cholesterol (total C), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) compared to placebo at weeks 24 and 48. The below table is the percent change from baseline with 95% confidence intervals at 36 weeks.

| | Placebo | 1 mg | 4 mg (2 mg start) | 4 mg (4 mg start) | 8 mg (2 mg start) | 8 mg (4 mg start) | 12 mg |
|---|---|---|---|---|---|---|---|
| **Trigly,** | 1.4 (-9.3, 12.1) | -18.9 (-25.1, -10.8) | -33 (-39.4, -26.5) | -34.9 (-46.2, -23.6) | -43.6 (-50.1, -37.1) | -37.2 (-44.5, -29.9) | -39.9 (-46.7, -33.1) |
| **Total C** | 1.9 (-1.5, 5.2) | -4.5 (-8.0, -1.0) | -12.6 (-17.0, -8.3) | -10.0 (-15.8, -4.3) | -18.2 (-22.2, -14.1) | -13.9 (-17.8, -9.9) | -17.8 (-21.5, -14.2) |
| **LDL** | -0.3 (-5.0, 4.4) | -4.7 (-9.3, -0.1) | -14.5 (-20.7, -8.3) | -10.2 (-17.6, -2.8) | -20.7 (-26.1, -15.3) | -16.8 (-22.2, -11.5) | -21.7 (-27.2, -16.2) |
| **VLDL** | 1.7 (-9.0, 12.4) | -17.2 (-24.3, -10.0) | -32.7 (-39.2, -26.3) | -35.0 (-46.2, -23.7) | -43.4 (-50.0, -36.8) | -36.7 (-43.9, -29.4) | -38.8 (-45.7, -31.8) |

Rosenstock et al., 2023, a study in patients with type 2 diabetes, also included blood pressure and lipid profiles as exploratory outcomes. Systolic and diastolic blood pressure decreased in all retatrutide groups; the differences were significant for systolic blood pressure reductions for the 8 mg (starting dose 4 mg) and the 12 mg dose groups. Systolic blood pressure increased slightly from baseline in the

placebo group (1.49 mmHg, standard error (SE)=2.08), whereas systolic blood pressure decreased by up to -8.79 mmHg (SE=1.47) in the 12 mg retatrutide group. Diastolic blood pressure decreased from baseline in the placebo group (-1.16 mmHg SE=1.03) but decreased significantly more in the higher dose retatrutide groups – up to -3.89 mmHg (SE=0.88). Lipid profiles also improved in a dose-dependent manner; total cholesterol (up to -16.67% retatrutide vs. -2.23% placebo), non-HDL cholesterol (up to -20.71% retatrutide vs. -3.9% placebo), triglycerides (up to -35.02% retatrutide vs. -9.89% placebo), were all significantly decreased in the 8 and 12 mg groups compared to placebo. The study did report increases in heart rate in retatrutide treated patients.

A phase 1b study of retatrutide in 72 patients with type 2 diabetes also reported reductions in both systolic and diastolic blood pressure in patients who received retatrutide, as well as increases in pulse rate and improvements in lipid profiles (Urva et al., 2022)

**Safety:** Retatrutide is associated with GI events. These events are common, though often mild. Rare but serious events including increased liver enzymes, cardiac arrhythmias, pancreatitis, and cholecystitis have been observed in some but not all trials.

*Types of evidence:*

- 1 meta-analyses or systematic reviews
- 3 clinical trials
- 1 textbook chapter
- 1 laboratory study

Thus far, retatrutide appears to be associated with mild to moderate gastrointestinal adverse events, particularly during dose escalation. These adverse events may be mitigated by use of a lower starting dose.

Jastreboff et al., 2023 details a Phase 2 RCT of retatrutide in 338 patients with obesity or overweight. Patients were randomized to either placebo or 1, 4, 8, or 12 mg of retatrutide once weekly. The 4, 8, and 12 mg groups were split into two subgroups with different initial doses to test different dose escalation protocols. Overall, adverse events were more common in the higher dose groups, particularly if they started at a higher dose. The incidence of serious adverse events was similar between groups. Nausea,

diarrhea, vomiting, constipation, decreased appetite, early satiety, fatigue, increase in lipase levels, and COVID-19 were all reported in 5% or more of patients.

Transient increases in alanine aminotransferase levels more than 3 times the upper limit of normal range were observed in 1% of patients who received retatrutide. Increases in amylase and lipase levels were asymptomatic except for one serious adverse event of pancreatitis in the 12 mg retatrutide group. In the retatrutide group, the heart rate increased in a dose-dependent manner up to 24 weeks and then declined. There were numerically more cardiac arrhythmias in the retatrutide group; they were mild to moderate in severity except for one serious adverse event of prolonged QT syndrome in 1 patient in the 12 mg retatrutide group. Cutaneous hyperesthesia and skin sensitivity adverse events were more common in patients who received retatrutide compared to placebo; none of these events were severe or serious, and they did not lead to discontinuation of treatment.

| | Placebo | 1 mg | 4 mg (2 mg start) | 4 mg (4 mg start) | 8 mg (2 mg start) | 8 mg (4 mg start) | 12 mg (2 mg start) |
|---|---|---|---|---|---|---|---|
| **Any AE** | 70% | 84% | 73% | 85% | 80% | 94% | 92% |
| **Serious AE** | 4% | 4% | 0% | 6% | 3% | 6% | 3% |
| **AE Leading to Discontinuation** | 0% | 7% | 6% | 9% | 14% | 6% | 16% |
| **Nausea** | 11% | 14% | 18% | 36% | 17% | 60% | 45% |
| **Cardiac arrhythmia** | 3% | 4% | 0% | 6% | 0% | 14% | 11% |

There was one death in the study; a patient who received retatrutide died by drowning, and the death was determined to be unrelated to study drug. There were not cases or clinically significant hypoglycemia, medullary thyroid cancer, or C-cell hyperplasia.

These safety results include the substudy population detailed in Sanyal et al., 2024, which assessed the effects of retatrutide in patients with MASLD. There were no signs of hepatotoxicity in either the overall study or substudy.

Rosenstock et al., 2023 reports on a 36-week Phase 2 RCT of retatrutide in 281 patients with type 2 diabetes. Patients were randomized to either placebo, dulaglutide (1.5 mg), or retatrutide treatment. The patients randomized to retatrutide were further randomized to 6 dosing groups: 0.5 mg, 4 mg

(starting dose 2 mg), 4 mg (starting dose 4 mg), 8 mg (starting dose 2 mg), 8 mg (starting dose 4 mg), or 12 mg (starting dose 2 mg). The trial also tested different dose escalation protocols. Generally, incidence of treatment-emergent adverse events was higher in higher doses of retatrutide compared to placebo. Discontinuations due to adverse events were more common in the retatrutide groups compared to placebo. The incidence of serious adverse events was similar between groups. Three serious adverse events in the retatrutide group were ascribed to study drug: one case of cholecystitis (8 mg starting dose 4 mg group); one case of acute pancreatitis (8 mg starting dose 2 mg group; this event happened 1 week after the initial and only dose); and one case of diabetic and starvation ketoacidosis (in the 12 mg group). There were no deaths in the study.

The most common adverse events were gastrointestinal events, including nausea, diarrhea, vomiting, decreased appetite, and constipation. These were more frequent in higher dose groups, and in groups that started at higher doses. Most of these events were mild to moderate in nature. Other events that were reported by at least 5% of participants included COVID-19, headache, increase in lipase levels, and urinary tract infection.

| | **Placebo** | **0.5 mg** | **4 mg (2 mg start)** | **4 mg (4 mg start)** | **8 mg (2 mg start)** | **8 mg (4 mg start)** | **12 mg (2 mg start)** | **Dulaglutide (1.5 mg)** |
|---|---|---|---|---|---|---|---|---|
| **Any AE** | 62% | 55% | 57% | 79% | 73% | 71% | 76% | 67% |
| **Serious AE** | 7% | 6% | 4% | 8% | 8% | 4% | 4% | 2% |
| **AE Leading to Discontinuation** | 4% | 2% | 0 | 4% | 12% | 17% | 15% | 1% |
| **Nausea** | 4% | 4% | 9% | 25% | 27% | 42% | 20% | 17% |

Three cases of moderate hypoglycemia were reported: one apiece in the 4 mg, 8 mg (starting dose 2 mg), and 12 mg group. There were no cases of severe or serious hypoglycemia, severe persistent hyperglycemia, thyroid malignancies, or C-cell hyperplasia. Liver enzymes generally decreased from baseline.

A 12-week study in 72 patients with type 2 diabetes similarly found that diarrhea and nausea were the most frequently reported treatment-emergent adverse events and were more common in the dulaglutide and retatrutide groups. Most events were mild to moderate in nature and resolved within approximately 10 days after onset without treatment interruption. The events were more common in

higher dose groups. There were a total of 4 patients who reported serious adverse events; none were in the higher retatrutide dose groups. There was one death due to a motor vehicle accident. A total of four patients discontinued due to treatment-emergent adverse events. Two were considered to be related to study drug; one was an adverse event of diarrhea in the 1.5 mg retatrutide group, and another was nausea in the 3/6/9/12 group after the 6 mg dose at week 4. There were no treatment-emergent adverse events of special interest to incretin agents, including pancreatitis, severe persistent hypoglycemia, thyroid malignancies, C-cell hyperplasia, cardiovascular events, severe gastrointestinal events, or acute renal events, among others. Mean liver enzyme levels decreased over the course of the trial in all groups except for dulaglutide (Urva et al., 2022).

***Drug interactions***:

The drug interactions of retatrutide are not yet fully known. Given the partly overlapping agonism, retatrutide 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, 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 retatrutide and other triple agonists. 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 retatrutide as well, and whether there are additional interactions or other nuances specific to the triple agonists.

**Research underway:**

There are 10 clinical trials that are currently ongoing and involve retatrutide registered on clinicaltrials.gov. All the studies involve patients with type 2 diabetes and/or have overweight or obesity. The studies are looking at a variety of outcomes, including glycemic control, weight loss, cardiovascular

outcomes, and renal function. Some trials are comparing retatrutide to approved drugs like semaglutide or tirzepatide.

There are no registered trials that are assessing the effects of retatrutide on cognition or dementia.

**Search terms:**

Pubmed, Google: retatrutide, LY3437943

- Diabetes, obesity, MASLD, MASH, dementia, Alzheimer's disease, blood-brain barrier

Websites visited for retatrutide:

- Clinicaltrials.gov
- WebMD.com
- PubChem
- DrugBank.ca
- Cafepharma