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WHITEPAPER

The Past, Present, and Future of GLP-1 Agonists

AN EXPLORATION OF OBESITY AND BEYOND

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In the US, nearly 2% of all adults (~5 million) are estimated to be currently using a GLP-1 (glucagon-like peptide-1) medication, and this is expected to climb to 6% (~15 million adults) by 2030 (1).

GLP-1 receptor agonists, which are pharmacologic molecules that mimic a subgroup of gut-derived peptide hormones called incretins, have been commercially available for nearly two decades since the FDA approved Byetta (exenatide) for type 2 diabetes in 2005 (2). Their demand, however, has soared over the past few years with the emergence of next generation GLP-1 treatments which have demonstrated unprecedented efficacy in weight loss. In clinical trials, non-diabetic overweight/obese patients given Novo Nordisk's Wegovy (semaglutide), were able to shed ~12% of their starting weight, and patients treated with Eli Lilly's recently approved GLP-1 for obesity, Zepbound (tirzepatide), achieved ~20% reduction in weight (3, 4). Naturally, attention around these new obesity drugs have gone mainstream, with celebrities and influencers promoting their weight loss effect on social media (5). Meanwhile, stakeholders in healthcare have increasingly focused on managing appropriate use of GLP-1 medications to ensure available supply (6). **"G-drugs"** (agents with agonist activity at any combination of GLP-1 receptors, GIP (glucose-dependent insulinotropic polypeptide) receptors and GCG (glucagon) receptors)) comprise a highly competitive clinical pipeline (>65 currently active programs; **Figure 1**). Given that this pipeline spans combination treatments and a growing list of indications beyond diabetes and obesity, the therapeutic impact of this class of drugs is bound to evolve significantly over the next decade. In this white paper, we explore the current issues surrounding GLP-1 therapies, their potential to treat a multitude of conditions, and where the landscape is headed as it continues to catalyze unanticipated changes in medicine.

Recent Trends in GLP-1 Use in the US

Even before Wegovy came to market in June 2021 (with an indication for obesity), use of Ozempic (indicated for diabetes) in non-diabetic obese patients had been steadily increasing. Whereas 4% of new patients prescribed Ozempic had an obesity diagnosis without a diabetes/prediabetes diagnosis in 2018 (one year after Ozempic's launch), this had climbed to 13% by 2021 (7). This trend appears to have continued after Wegovy became available, with ~34% of new patients prescribed a diabetes-indicated GLP-1 (between January 2021 and May 2023, commercial payer channels) having a diagnosis other than diabetes (6). On the prescriber side, from July 2020 to May 2023, the total number of US providers writing GLP-1 prescriptions increased by 228%. This was driven by specialists other than endocrinologists and diabetes specialists, which suggests an increasing comfort level in primary care.

Coverage and Access to GLP-1 Medications

While patient requests and provider prescribing of the new G-drugs have surged, payers have been clamping down to limit off-label use. The share of claim rejections for GLP-1 therapies increased from 30% before Wegovy's launch to 41% after Mounjaro's (tirzepatide) launch in May 2022 (6). Employers have also increasingly restricted or altogether eliminated coverage of the weight-loss medications: as of September 2023, less than half (42%) of large employers covered GLP-1s for the treatment of obesity, with the majority requiring prior authorization for both diabetes and obesity, and sometimes beyond the FDA label (8).

For both commercial and government-sponsored health plans, the cost of covering GLP-1s for weight loss is a critical issue, considering nearly 40% of adults and 20% of children in the US are obese (9). In addition, the estimated annual net price (i.e., after rebates and discounts) of Wegovy is nearly $14k, substantially higher than that of older weight loss medications such as generic phentermine-topiramate, which carries a net price of ~$700 per year (10). As commercial payers grapple with controlling the utilization of G-drugs, manufacturers are pushing for legislation to allow coverage of anti-obesity treatments under Medicare (11). Medicare currently offers coverage for services such as screening, behavioral counseling, and bariatric surgery for obesity; however, weight loss medications are excluded by law from Part B and Part D (though potential changes to this are being negotiated). Similarly in Medicaid, because weight loss drugs are part of a short list of medications that can be excluded from coverage under the Medicaid Drug Rebate Program, coverage of anti-obesity medications is provided by only 16 state Medicaid programs as of January 2024 (12, 13).

Given the high demand and high price of the new GLP-1 anti-obesity drugs, their potential coverage expansion under Medicare undoubtedly has significant implications. One study has estimated that if just 10% of Medicare beneficiaries with diagnosed obesity use Wegovy, the annual cost to Medicare could be $13.6 billion, representing >9% of Part D net spending (10). As a consequence, Medicare premiums will likely increase to accommodate spending on GLP-1s for weight management. Based on evidence that private insurance increases fees following Medicare fee hikes, this dynamic is also expected to spill over to commercial health plans (14).

Considerations for Long-Term Treatment

Weight management requires chronic treatment and realizing the long-term benefits of GLP-1 drugs will partly depend on patient compliance to the medications. Current evidence shows suboptimal compliance on GLP-1s among non-diabetic obese patients, with only about a third taking their medication one year after treatment initiation (15). Poor compliance and treatment discontinuation may not only result in financial waste for healthcare systems, but also reversal in the beneficial effects of the initial weight loss for patients. An extension analysis of Novo's STEP 1 study found that one year after stopping Wegovy, patients had regained two-thirds of the weight they had lost under treatment and also regressed towards baseline in cardiometabolic endpoints (16). Potential safety implications of long-term GLP-1 treatment, however, further complicate their risk/benefit profile. A real-world study of diabetic patients found increased risk of thyroid cancer with extended use of GLP-1 therapies (not including semaglutide or tirzepatide) (17). A recent study also reported higher risk of pancreatitis, gastroparesis, and bowel obstruction in GLP-1 users diagnosed with obesity (18). More post-marketing studies are needed to better understand the long-term tolerability and safety of these medications.

GLP-1: A Healthcare Provider's Swiss Army Knife

Pharmacologic use of GLP-1 analogues began in diabetes, where the molecule's therapeutic effect is primarily mediated through its interaction with GLP-1 receptors in the pancreas (19). GLP-1 receptors, however, are distributed across multiple tissue types, and this enables GLP-1 agonists to have a wide range of therapeutic applications. In weight management, for example, GLP-1 receptors in the brain are thought to facilitate the feeding inhibitory, or "anorexigenic" effect, of GLP-1 peptide. Delayed gut emptying is another physiologic effect of GLP-1 widely known to support glycemic control and may also help with weight loss. Outside of diabetes and weight management, more evidence is emerging indicating that GLP-1 therapies may have a transformative effect on overall health.

CARDIOVASCULAR DISEASE (CVD):

In clinical studies, semaglutide has demonstrated reduction in cardiovascular event risk in diabetics, and recently released results from the SELECT study indicate that this also translates to the non-diabetic overweight/obese population (20). While the CVD benefits of semaglutide are to some extent an indirect outcome of weight loss, they appeared earlier than weight loss, which may suggest that G-drugs can improve cardiovascular performance independent of decreases in body weight. Additionally, preclinical studies indicate that GLP-1-driven improvements in cardiovascular metrics may be linked to reduced inflammation, and this is consistent with the reduction in a key inflammatory marker, C-reactive protein (CRP), shown in the SELECT study. Beyond trials for cardiovascular risk reduction, our analysis shows 8 trials across 6 programs in heart failure **(Table 1).**

METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH):

In addition to diabetes and obesity, the most common indication being actively studied for G-drugs is MASH, with 34 trials across 16 programs **(Table 1)**. So far, both Novo and Lilly have shown that overweight/obese MASH patients administered subcutaneous GLP-1 (once-daily for semaglutide and once-weekly for tirzepatide) can achieve MASH resolution with no worsening of fibrosis – while semaglutide showed MASH clearance in 59% of patients at 72 weeks (vs. 17% in placebo), tirzepatide achieved this outcome in 74% of patients at 52 weeks (vs. 13% in placebo) (21, 22). Most recently, Boehringer Ingelheim and Zealand Pharma's survodutide (a GCG/GLP-1 dual agonist) not only demonstrated improvement of MASH in 83% of patients (18% in placebo) after 48 weeks, but also showed statistically significant improvements in liver fibrosis (23).

CHRONIC KIDNEY DISEASE (CKD):

Benefits in some kidney endpoints (such as albuminuria) have also been shown in a meta-analysis of GLP-1 therapies (in diabetics). The impact of these drugs on eGFR (estimated glomerular filtration rate) decline and progression to end-stage kidney disease has yet to be shown broadly in CKD, though semaglutide has shown a reduction in kidney disease progression in diabetics (24). Early signals of the effect of G-drugs on eGFR may come from Lilly's Phase 2b trial investigating the efficacy of its triple-G, retatrutide, in diabetic and nondiabetic CKD.

NEURODEGENERATIVE DISEASE:

GLP-1 agonists have also been found to improve brain glucose metabolism and exert neuroprotective effects in animal models of Alzheimer's disease (AD), Parkinson's disease (PD), and stroke, as well as in reducing chronic pain (19). In mouse models of AD, chronic treatment with liraglutide has been found to prevent memory loss and amyloid-beta accumulation, as well as reduce microglia-associated neuroinflammation (25). On the clinical side, AD patients treated with liraglutide for 12 months have shown improved cognitive function compared to placebo. Currently ongoing large-scale clinical studies such as Novo's Phase 3 EVOKE trial in early Alzheimer's may help us better understand the potential of G-drugs in AD. Studies in animal models of PD suggest that treatment with GLP-1 analogues may minimize loss of dopaminergic neurons (by inhibiting microglial activation), reduce alpha-synuclein accumulation, and improve motor function. On a promising note, PD patients treated with G-drugs have experienced some improvement in motor and non-motor function in small-scale Phase 2 studies. Though GLP-1 medications have so far been safe and well-tolerated in clinical studies of PD, their potential side effects are particularly important to consider in Parkinson's, as weight/muscle loss is a commonly experienced symptom of PD progression and may be exacerbated by GLP-1 use.

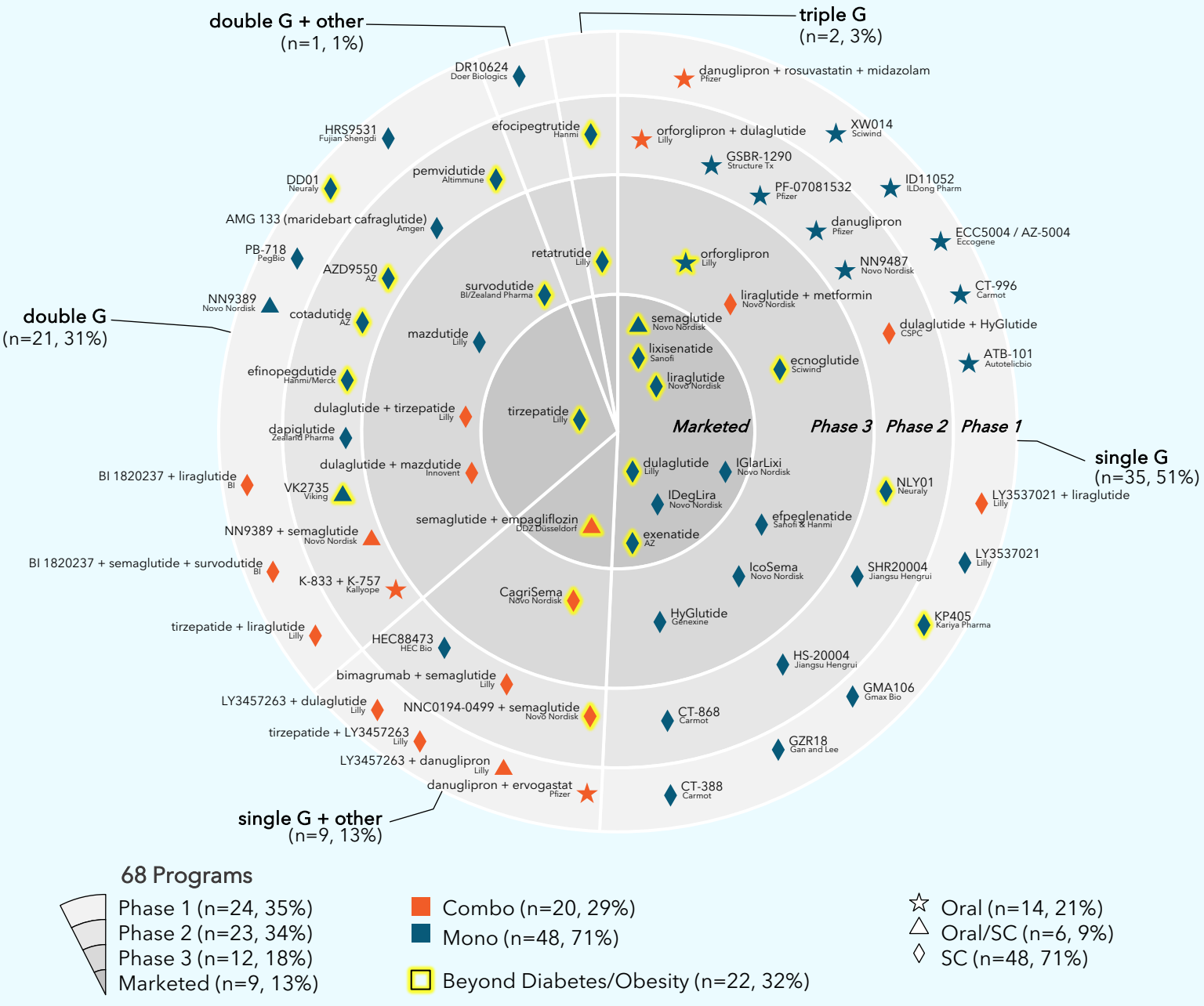
OTHER INDICATIONS:

The effect of G-drugs on consumption behavior also extends beyond food intake. Animal studies have shown that GLP-1 analogues suppress reward behavior like alcohol intake by targeting areas of the brain involved in pleasure, motivation, and addiction (19). Though robust clinical evidence is lacking in this area, users of Ozempic, Wegovy, and Mounjaro have self-reported reduced craving for alcohol and alcohol consumption, and (academic) clinical studies investigating the impact of GLP-1s on alcohol use disorder are underway (26). Other than reward behavior, the effect of G-drugs on emotional well-being and depression are also being studied. Intriguingly, meta-analyses have also suggested a G-drug effect in colorectal cancer in diabetics (whether overweight or not) (27).

Next Generation GLP-1 Treatments

Clinical development around G-drugs continues to expand as we learn more about their potential benefits. In our analysis, we have identified 68 currently active programs across more than 10 indications **(Figure 1)**.

Figure 1. Currently Active Programs for GLP-1-Targeting Agents



ClinicalTrials.gov, EvaluatePharma, accessed January 2024 (highest phase of development shown)

Table 1. Recently Completed and Ongoing Trials for GLP-1 Agents in Indications Beyond Diabetes and Obesity

COMPANY	PROGRAM	MOA	MASH	KIDNEY DISEASE	HEART FAILURE	NEURO-DEGENERATIVE DISEASE	OTHER
Altimmune	pemvidutide	GCGR/GLP-1	5	-	-	-	-
AZ	AZD9550	GCGR/GLP-1	2	-	-	-	-
AZ	cotadutide	GCGR/GLP-1	3	1	-	-	-
AZ	exenatide	GLP-1	1	-	-	1	-
BI/Zealand Pharma	survodutide	GCGR/GLP-1	1	-	-	-	-
DDZ Düsseldorf	semaglutide + empagliflozin	GLP-1 + SGLT2	1	-	-	-	-
Hanmi	efocipegtrutide	GIP/GCGR/GLP-1	2	-	-	-	-
Hanmi/Merck	efinopegdutide	GCGR/GLP-1	3	-	-	-	-
Kariya Pharma	KP405	GLP-1	-	-	-	1	-
Lilly	dulaglutide	GLP-1	1	-	-	-	-
Lilly	orforglipron	GLP-1	-	1	1	-	-
Lilly	retatrutide	GIP/GCGR/GLP-1	1	2	1	-	3
Lilly	tirzepatide	GIP/GLP-1	1	1	1	-	4
Neuraly	DD01	GCGR/GLP-1	1	-	-	-	-
Neuraly	NLY01	GLP-1	-	-	-	1	-
Novo Nordisk	CagriSema	GLP-1/AMY	-	1	1	-	-
Novo Nordisk	liraglutide	GLP-1	-	-	2	1	4
Novo Nordisk	NNC0194-0499 + semaglutide	FGF21 + GLP-1	2	-	-	-	-
Novo Nordisk	semaglutide	GLP-1	8	4	2	3	4
Sanofi	lixisenatide	GLP-1	-	-	-	1	-
Sciwind	ecnoglutide	GLP-1	1	-	-	-	-
Viking	VK2735	GIP/GLP-1	1	-	-	-	-
Total Number of Trials			34	10	8	8	15

ClinicalTrials.gov, EvaluatePharma, accessed January 2024
AMY, amylin; **FGF21**, fibroblast growth factor 21

In its pursuit to create an even more potent G-drug, Eli Lilly is developing the aforementioned retatrutide, the most advanced triple-G agonist which engages GLP-1 and GIP receptors like tirzepatide, as well as GCG receptors. Similar to GLP-1, GIP and GCG are associated with reduced food intake and decreases in body weight, and GIP is thought to exert its anorectic effects by acting on receptors in the brain (28, 29). In obese patients, retatrutide has not only demonstrated greater reduction in body weight (~24%) compared to semaglutide and tirzepatide, but also resolution of fatty liver disease in more than 85% of patients (30, 31). With resmetirom (a THβ agonist from Madrigal Pharmaceuticals) expected to launch this year and become the first approved treatment for MASH (and FGF21 analogues not far behind), this space is sure to be competitive in the near future.

Triple-G agents are not the only unique feature in the G-drug pipeline. 11 out of 68 (~16%) identified programs **(Table 2)**, involve combination regimens and 22 of 68 (32%) are being studied in indications which do not yet have an approved GLP-1 (e.g., MASH, neurodegenerative disease, heart failure) (Table 1).

Table 2. GLP-1 Programs with Combination MOAs

Combination Regimens (beyond G-drugs)		
Company	**Program**	**MOA**
Pfizer	danuglipron + ervogastat	GLP-1 + DGAT2
Novo Nordisk	CagriSema	GLP-1/AMY
Novo Nordisk	NNC0194-0499 + semaglutide	FGF21 + GLP-1
Lilly	bimagrumab + semaglutide	ACVR2 + GLP-1
Lilly	LY3457263 + danuglipron	NPY + GLP-1
Lilly	LY3457263 + dulaglutide	NPY + GLP-1
Lilly	tirzepatide + LY3457263	GIP/GLP-1 + NPY
HEC Bio	HEC88473	FGF21/GLP-1
Doer Biologics	DR10624	FGF21/GCGR/GLP-1
DDZ Düsseldorf	semaglutide + empagliflozin	GLP-1 + SGLT2

ClinicalTrials.gov, EvaluatePharma, accessed January 2024
AMY, amylin; **ACVR2**, activin type II receptor; **DGAT2**, diacylglycerol acyltransferase; **FGF21**, fibroblast growth factor 21; **NPY**, neuropeptide Y

One of the later stage combination treatments that has been drawing industry attention is CagriSema, Novo Nordisk's fixed dose combination of semaglutide and cagrilintide (cagrilintide is a long-acting analogue of amylin, a pancreatic hormone which can delay gastric emptying). CagriSema is yet another sign of increasing competition between Novo and Eli Lilly – as Lilly tries to demonstrate tirzepatide's weight loss superiority over semaglutide, Novo is conducting a head-to-head obesity trial of CagriSema against tirzepatide. Unsurprisingly, CagriSema is also under investigation in cardiovascular disease as well as kidney damage in diabetic overweight/obese patients.

The next wave of GLP-1s is not limited to injectable medications – 20 oral G-drug programs are also in the pipeline. In addition to retatrutide, Lilly is currently developing orforglipron, a once-daily oral GLP-1 capsule. In Phase 2 studies, participants treated with orforglipron were able to lose ~15% of body weight on average (32). Though they may be slightly less potent, oral G-drugs could potentially overcome the compliance issues seen with their injectable counterparts. Both CagriSema and orforglipron are expected to quickly become blockbuster drugs: EvaluatePharma estimates 2028 US sales for CagriSema and orforglipron at $5.2B and $2.9B respectively (33).

The Next Wonder Drug?

Wall Street analysts expect annual sales of G-drugs to reach $100 billion by 2030, making it one of the biggest blockbuster classes in history (34). While true analogues may not exist, a parallel can be found in statins, long-term medications which also have a massive treatment-eligible population. A key differentiator, however, is that statins mainly target lipid production, while GLP-1 agonists can exert a broad range of pharmacologic effects across various tissue types and potential indications. Of course, obesity by itself comprises a large population, and while allowing this many patients to access effective anti-obesity medications will lead to short-term increases in drug spending, there are also possibilities of long-term social benefit. Considering the many comorbidities and overall reduced quality of life associated with obesity, some estimates suggest total potential healthcare savings of $1 trillion over 10 years if all eligible patients in the US gained access to weight-loss treatments (35). The possibility of widespread access to these drugs currently remains unclear – regardless, GLP-1s will likely alter the course of the US obesity epidemic with the potential to go far beyond it.

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