

## GLP-1 RECEPTOR AGONISTS: A POTENTIAL KEY TO LONGEVITY?



*“New interventions can tempt modellers to don blinkers, focusing too narrowly and risking inaccuracy – especially for treatments with broad health implications, like those affecting the biological aging process itself.”*

Ashley Campbell, Director

### The real-world challenges of breakthrough

GLP-1 receptor agonists (RAs) have been an important add-on treatment for obese people with type II diabetes for nearly two decades. Recent clinical trial successes in non-diabetic people with complications of obesity – coupled with a significant social media buzz – have given rise to a burgeoning industry for these treatments, anticipated to surpass \$2 billion in 2023.<sup>1</sup>

#### Increasing health inequalities

The surging demand and subsequent shortages have given rise to health inequalities. Those who need these drugs as a diabetes intervention are facing shortages due to their off-label use for weight loss.<sup>1</sup> The higher cost and weekly injection regimen of drugs like semaglutide (Ozempic®, Rybelsus®, Wegovy®) present significant barriers to uptake. Overall, the socioeconomic mortality gap may widen as a result, as longevity benefits concentrate among the more affluent.

*“While GLP-1 RAs hold promise for improving mortality rates, modelers must consider the current challenges of cost, access, and method of delivery when evaluating their short to medium-term impact on life expectancies.”*

#### Role in Obesity Epidemic

The global obesity pandemic affects nearly two billion individuals worldwide, and over a quarter of adults in England are considered obese.<sup>2</sup> Its prevalence and the accompanying suite of chronic conditions – like heart disease and diabetes – pose a significant burden on healthcare systems. GLP-1 RAs have emerged as a dual-force, combating both diabetes and obesity by mimicking GLP-1's hormonal action to regulate blood sugar and appetite. The STEP 1 clinical trial has highlighted the capability of semaglutide to effectuate an approximate 12% reduction in body weight,<sup>3</sup> meriting its endorsement by the NHS for weight management.<sup>4</sup> Unfortunately, the widespread adoption of these treatments is currently hampered by the necessity for weekly injections, leading to limited delivery. This may change in the future with oral formulations such as Rybelsus® becoming available, increasing uptake.

## Lifting the blinkers

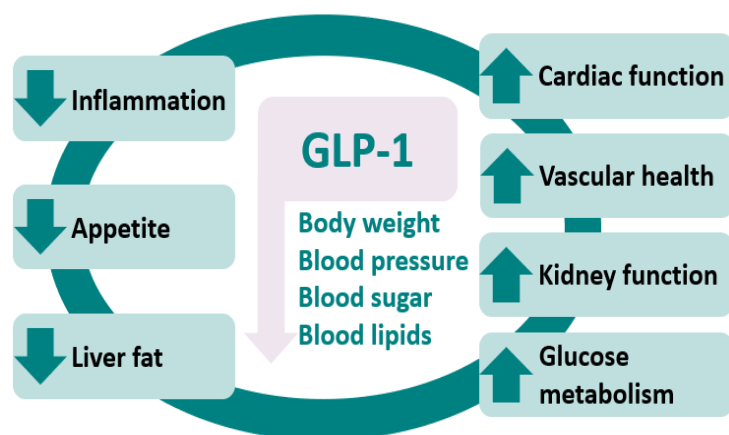
*“GLP-1 RAs have emerged as prime candidate drugs for slowing the aging process. Longevity modelers should incorporate the potential of these drugs to extend healthy life spans and delay the onset of age-associated conditions, which could significantly alter future longevity scenarios and risk assessments.”*

Understanding the mechanisms of action of treatments like GLP-1 RAs is vital when modelling the potential effects on future longevity. The potential impact of GLP-1 RAs arises from the biochemical processes which they target, rather than the specific disease indications for which it is approved. Basing a model simply on the mortality effect on the target disease as opposed to the global effects, both positive and negative, is less likely to be accurate.

### Target aging mechanism – Nutrient sensing

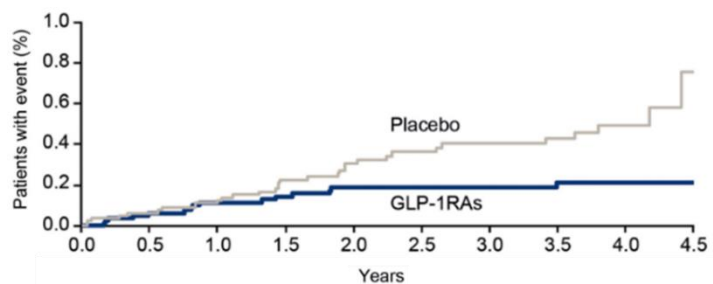
Nutrient sensing pathways are systems that are critical to how our bodies process food for energy and maintenance. Over time these systems deregulate or break down, leading to problems like obesity, diabetes, cardiovascular disease and other age-related diseases.

GLP-1 acts to regulate glucose concentrations in the blood by stimulating insulin release, reducing nutrient absorption, and reducing appetite. Disruption in nutrient sensing pathways is one of the drivers of the ageing process, and GLP-1 RAs are therefore prime candidate drugs for slowing the ageing process.



### Impact on aging-related diseases

GLP-1 RAs have already been shown to improve cardiac and kidney function, and reducing cardiovascular disease mortality by 14% amongst diabetic patients.<sup>5,6</sup> Investigations are also exploring their impact on early Alzheimer’s disease. In three clinical trials a nationwide cohort study, researchers discovered that individuals with type II diabetes who were treated with GLP-1 RAs experienced a significant reduction in the risk of developing dementia.<sup>7</sup>



The broad impact of GLP-1 RAs on various age-related disease outcomes highlights their potential beyond diabetes management, suggesting their potential as a ‘gero-therapeutic’ restoring nutrient sensing balance. Nonetheless, distinguishing their direct anti-aging effects from their ability to mitigate specific pathologies, such as Type II diabetes, remains challenging.

## Crystallise's insights & expertise

At Crystallise, we delve into the complexities of these emerging therapies with a keen eye for their implications for the insurance industry. Our research into this and other “hallmarks of aging” is bringing new understanding to the way in which we view the impact of future biomedical advancements in longevity. If you would like to hear more about this or our many other areas of research, please feel free to reach out.

---

### References:

1. CNN. (2023). *Shortage of popular diabetes drug after celebrities, TikTok users say it helps with weight loss*. Available at: <https://www.cnn.com/2023/03/17/health/ozempic-shortage-tiktok-telehealth/index.html>
2. Caballero, B. (2019). *Humans against obesity: who will win?* *Advances in Nutrition*, 10(1), S4–S9. doi: 10.1093/advances/nmy055. Available at: <https://academic.oup.com/advances/article/10/1/S4/5307224>
3. Wilding, John P.H., Rachel L. Batterham, Salvatore Calanna, Melanie Davies, Luc F. Van Gaal, Ildiko Lingvay, and others, 'Once-Weekly Semaglutide in Adults with Overweight or Obesity', *New England Journal of Medicine*, 384.11 (2021), 989–1002. <https://doi.org/10.1056/NEJMoa2032183>
4. National Institute for Health and Care Excellence (NICE). *Semaglutide for managing overweight and obesity*. Available at: <https://www.nice.org.uk/guidance/ta875>
5. Koliaki, C., & Doupis, J. (2011). *Incretin-based therapy: a powerful and promising weapon in the treatment of type 2 diabetes mellitus*. *Diabetes Therapy*, 2(2), 101–121. doi: 10.1007/s13300-011-0002-3.
6. Caruso, I., et al. (2022). *Cardiovascular and Renal Effectiveness of GLP-1 Receptor Agonists vs. Other Glucose-Lowering Drugs in Type 2 Diabetes: A Systematic Review and Meta-Analysis of Real-World Studies*. *Metabolites*, 12(2), 183. doi: 10.3390/metabo12020183. Available at: <https://www.mdpi.com/2218-1989/12/2/183>
7. Nørgaard CH., et al. (2022) *Treatment with glucagon-like peptide-1 receptor agonists and incidence of dementia: Data from pooled double-blind randomized controlled trials and nationwide disease and prescription registers*. *A&D Transl Res & Clin Interv*. 2022 Jan;8(1):e12268. <https://doi.org/10.1002/trc2.12268>.



*Crystallise Ltd*

---

Follow us:



Email: [contact@crystallise.com](mailto:contact@crystallise.com)

Website: [www.crystallise.com](http://www.crystallise.com)