The Altascientist

SCIENTIFIC JOURNAL

ISSUE NO. 48

THE EVOLVING LANDSCAPE OF METABOLIC RESEARCH

From GLP-1 to Multifunctional Agonist Therapy

GLP-1s have been a major factor in the treatment of certain metabolic conditions since the early 2000s, with generics of the first medications now coming onto the market. Initially indicated for Type 2 diabetes (T2D) with the launch of exenatide in 2005, current indications include body weight reduction, reduction of risk of major cardiovascular (CV) events, and treatment of non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH), formerly known as non-alcoholic steatohepatitis (NASH).

Ongoing research is generally focused on improvement of patient experience with reduced side effects, more convenient administration options, and developing new indications for current molecules. Research on next-generation and companion molecules is also a key focus of today's development landscape.

IN THIS ISSUE

Approaching the topic from the perspective of an expert, integrated drug development organization (DDO: CRO/CDMO) with decades of relevant experience, this article reviews the status of the market and touches on where we expect to see the field expanding in the coming years.

We also include a program overview case study demonstrating how Altasciences accelerated a recent early-phase GLP-1 program by six months compared to industry standard timelines.

THE EVOLUTION OF GLP-1 THERAPIES TO MULTI-AGONIST INCRETIN TREATMENTS

From Discovery to Development

The development of incretin-based therapies grew out of the discovery of the "incretin effect" in the 1960s. The incretin effect was the discovery that oral glucose ingestion triggers significantly higher insulin secretion than intravenous glucose. This process, mediated by intestinal hormones—GIP (isolated in the 1970s) and GLP-1 (characterized in the 1980s)—enhances insulin secretion in a glucose-dependent manner.

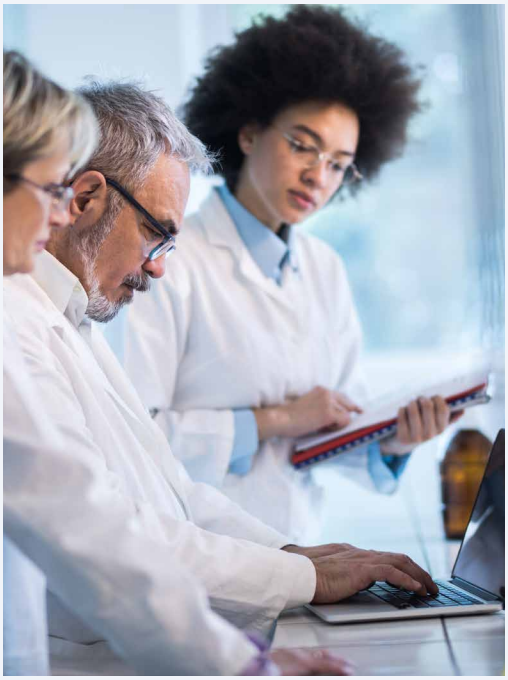
Research between the 1960s and 1980s revealed that the incretin effect is significantly impaired or lost in patients with T2D, highlighting its role in the disease's pathophysiology. These findings shifted the understanding of glucose metabolism from purely pancreatic control to include critical gut-pancreas signaling, paving the way for modern incretin-based therapies (DPP-4 inhibitors and GLP-1 receptor agonists) and future generations of incretin-based therapeutics.

Current Landscape: Expanding the Clinical Horizon of Incretin Therapies

While GLP-1 therapies remain foundational, novel mechanisms of action are actively being researched to complement or outperform existing options. These next-generation candidates aim to improve the efficacy and side effect profiles of GLP-1s and related treatments, reducing patient burden, and making the medications accessible to a wider range of patients.

As our scientific understanding deepens, regulatory agencies are expected to request additional and more specialized trials, expanding the scope of research to new indications, while deepening the study of obesity and diabetes. Emerging and ongoing areas of investigation include:

- Cardiovascular, liver, and renal outcomes
- Type 1 diabetes
- Addiction and reward-related pathways
- Cognitive health



GLP-1 receptors are widely expressed in the brain, including regions involved in learning, memory, and appetite regulation. Activation of these receptors appears to enhance neuronal survival, reduce neuroinflammation, and improve synaptic plasticity. These effects are particularly relevant because chronic inflammation and impaired neuronal signaling are central features of cognitive decline and neurodegenerative disease.

While recent trials have not demonstrated cognitive improvement in patients, there is ongoing research into whether GLP-1–based therapies may prevent or slow disease onset, the effects of which are not yet fully measurable and will require longer-term, innovative trial designs.

Key Neurological Effects Under Ongoing Study

The impacts of GLP-1s on neurological and cognitive health are in early stages of research, as real-world analysis indicates both positive and negative effects of GLP-1s, especially with long term use.

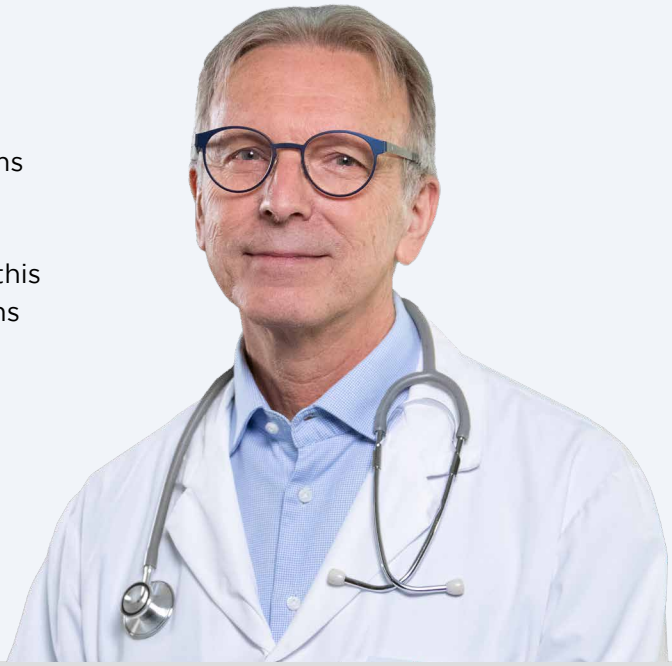
- **Neuroprotection:** Reduces neuroinflammation, oxidative stress, amyloid plaques, and neuronal injury, with a potential effect in Alzheimer's/Parkinson's diseases.
- **Cognition and Mood:** Potential for improving memory and attention; may alleviate depression symptoms but can also induce anxiety and depression.
- **Addiction and Reward:** Modulates the brain's reward system, impacting cravings for food, alcohol, and nicotine, but may also reduce positive emotions and interests.
- **Sensory Changes:** May alter taste perception and cause olfactory issues.
- **Cerebrovascular:** Shows promise in reducing stroke risk, intracranial pressure, and pain in conditions like migraine.

Interest in GLP-1 neurological effects is high, and the complexity of research exploring both their significant therapeutic potential (e.g. Alzheimer's, Parkinson's) and less understood paradoxical effects, like brain fog or mood changes, necessitates more robust studies.

Ongoing Research Goals for Incretin-Based Therapeutics

In addition to the growing interest in neurological effects, ongoing research on future GLP-1 therapeutics is focused on addressing multiple unmet needs, including improved tolerability, meaningful weight loss without sacrificing muscle and more accessible dosing formats. Overcoming weight-loss plateaus is another research focus; in other words, addressing common reasons for treatment failures and diminished efficacy over time, which is a common challenge with currently approved therapies.

> Having been involved in the development of incretin-based therapeutics since the inception of GLP-1 medications, the teams at Altasciences developed a level of expertise that accelerates sponsor programs while maintaining the highest levels of scientific rigor and data integrity. The case study presented in this issue of The Altascientist is just one example of recent programs which reduced the IND-enabling timeline by six months."
>
> — **Dr. Gaetano Morelli**, MD, FRCPC, ABIM, FACG,
> Executive Vice President of Medical Affairs
> and Chief Medical Officer at Altasciences



CASE STUDY PROGRAM OVERVIEW: ACCELERATED EARLY-PHASE END-TO-END SUPPORT OF GLP-1 RA THERAPEUTIC DEVELOPMENT.

Objective:

A biotech was developing a long-acting, subcutaneous injection of a GLP-1 for obesity and metabolic diseases. The sponsor needed to achieve critical scientific and operational milestones significantly faster than conventional timelines allow, while maintaining scientific precision and regulatory conformity.

The goal was to accelerate IND-enabling studies and streamline early clinical transitions under tight timelines and financial constraints. The Altasciences Acceleration Platform reduced program duration by 6 months, from preclinical through Phase I first-in-human (FIH) trials to Phase II efficacy and tolerability trials.

Integration Approach:

- Integrated preclinical and clinical planning to support both subcutaneous and oral formulations.
- Leveraged Altasciences' harmonized preclinical network for rapid model selection and dose optimization.
- Conducted proactive bioanalytical method development for cross-species PK and immunogenicity assessments.
- Maintained consistent oversight from preclinical through SAD/MAD phases, using real-time data visibility to guide dose escalation, highly adaptive protocol strategy, and aggressively driving to POC.

Phase I: Adaptive FIH Study of GLP-1 RA in Healthy Overweight Adults

Study Overview

- **Objective:** Assess safety, tolerability, PK/PD of single and multiple ascending doses, respecting a 6-month timeline.
- **Design:** Randomized, double-blind, placebo-controlled with SAD and MAD parts in 116 healthy adults with BMI 27–38 kg/m^2.
- **Dosing:** Single ascending doses and weekly multiple ascending doses over five weeks.

Operational Highlights

- Adaptive design with overlapping cohorts and rapid dose escalation.
- Tightly scheduled Safety Review Committee meetings for real-time safety and PK data evaluation.
- Close coordination between clinical research unit, bioanalytical labs, data services, and sponsor, tightly orchestrated by program management.

Key Findings

- No severe or serious adverse events (SAEs) and no participant withdrawals due to adverse events. Expected mild gastrointestinal adverse events consistent with GLP-1 RA profile.
- Drug half-life successfully characterized via LC-MS.
- Observed preliminary weight loss, confirming PD activity.

Phase I Outcome

Altasciences' adaptive design, operational excellence, and integrated team approach enabled rapid, safe dose escalation and robust PK/PD data generation, meeting the sponsor's aggressive timelines and supporting progression to Phase II.

Phase IIa: Dose-Dependent Efficacy and Tolerability Study in Participants With Obesity

Study Overview

- **Objective:** Evaluate 12-week safety, tolerability, and efficacy of the injectable in overweight/obese adults without T2D.
- **Design:** Randomized, double-blind, placebo-controlled, 5 cohorts of 24 participants each.
- **Dosing:** Weekly doses at 0.6, 0.8, 1.0, 1.2 mg, plus one cohort with dose escalation (0.4 → 0.8 → 1.2 mg).
- **Post-treatment:** At week 13, step-up dosing assessed tolerability of monthly dosing.

Key Findings

- Weight loss was dose-dependent; up to 11.3% placebo-adjusted mean body weight reduction in the 1.2 mg cohort.
- Individual responses reached nearly 20% weight loss.
- Weight loss plateau not reached, indicating potential for further reductions with longer treatment.
- Gastrointestinal adverse events were mild/moderate and transient.
- Dose escalation cohort showed excellent tolerability and clinically meaningful weight loss (6.3% placebo-adjusted).
- Pharmacokinetics demonstrated ~4-fold drug accumulation over 12 weeks, supporting titration-free dosing.
- Step-up to monthly dosing was well tolerated, validating the long-acting profile.

Operational Highlights

- Three sites were proactively prepared, working in unison to be able to start immediately after the top-line results of the Phase I Study were available.
- Database cleaning and key readouts occurred approximately two weeks after the last participant's last dose.

Phase II Outcome

Data suggests that the test article could be foundational for obesity treatment with flexible dosing options. Strong safety and efficacy signals support continued development.

Conclusion—Altasciences' Unique Contributions

Altasciences delivered a seamless transition across Phase I and IIa studies by:

- **Phase I:** Implemented adaptive designs with overlapping cohorts, real-time data reviews, and rapid sample analysis turnaround.
- **Phase IIa:** Executed complex dosing cohorts and step-up schemes with robust safety and efficacy monitoring.

The accelerated pathway provided the sponsor with the early PK/PD data to refine their formulation strategy, support internal funding decisions, and strengthen their competitive position within the incretin therapeutic landscape. By eliminating unnecessary gaps and advancing scientific work in parallel, the company reached critical development milestones months before they otherwise could have, thereby enhancing both program momentum and strategic optionality.

Development Phase	Industry Typical Duration	Altasciences Accelerated for Client
Safety Assessment (IND-enabling)	9-15 months	9 months
IND/CTA Preparation and Clearance	3-6 months	~2.5 months
Phase I (SAD/MAD Topline)	6-12 months	7 months
POC/POC-Equivalent (Topline)	9-18 months	6 months (12-weeks PD)
Safety Start to **Phase I Topline**	**18-36 months**	**17 months**
Safety Start to **POC/POC-Equivalent Topline**	**27-51 months**	**22 months**

Services Used

- Preclinical
- Clinical
- Bioanalytical
- Regulatory
- Program Management
- CRO Support

Dr. Morelli sees a bright future. "We are witnessing just a glimpse into the pipeline of anti-obesity medication development as we endeavor to manage the relentless epidemic of obesity. Decades of research are giving us a better understanding of the complexity of human weight regulation. We are on the cusp of witnessing the fruits of this labor.

Beyond incretins, research is now exploring novel pathways that will be more efficacious and targeted for obesity and related comorbidities. In this era of personalized therapy and precision medicine, the use of biomarkers or clinical characteristics will contribute to reliably predict individual response to guide personalized therapy."

LOOKING AHEAD: GLP-1 COMBINATIONS, COMPANION MOLECULES, AND MULTI-AGONIST INCRETIN THERAPIES

In 2026, drug development stakeholders in weight loss and metabolic health are devoting significant resources to studies that combine GLP-1 receptor agonists with other companion molecules to amplify weight loss, increase energy expenditure, or reduce muscle loss.

Incretin-based multi-agonists are a new generation of medications that activate two or more hormone receptors in a single molecule, providing superior metabolic benefits compared to traditional single-receptor drugs. Combining multiple receptor agonists can increase calorie burning in addition to reducing food intake, resulting in superior weight loss efficacy compared to GLP-1 alone. Emerging evidence also suggests that combinations and other companion molecules offer higher potential for treating and preventing fatty liver disease (MASH/NASH), cardiovascular risks, and possibly neurodegenerative disorders.

According to data from ClinicalTrials.gov, the number of registered studies across all incretin-based therapies has grown significantly, with the U.S. and China leading the volume of active trials. Recent years have seen more than 30,000 new study registrations annually across all medical fields, with GLP-1 and multi-agonist metabolic drugs representing a substantial and growing portion of those in the metabolic disease space.

As of February 2026, there were dozens of active clinical trials exploring multi-agonist incretin therapies, from early-phase pipeline to major Phase III programs. This surge in activity shows that 2025 to 2026 is the peak period for this drug class, and additional life-changing treatments are expected to become available in the near future.

THE IMPACT OF INCRETIN-BASED THERAPEUTICS ON THE GLOBAL PHARMACEUTICAL MARKET AND HUMAN HEALTH

From a human health perspective, incretin-based therapies have transformed outcomes for millions of patients by effectively delivering improved glycemic control and promoting meaningful weight reduction. Clinical trials continue to show additional health benefits and reduced overall mortality risk, positioning these agents as disease-modifying therapies rather than purely symptomatic treatments.

Economically, GLP-1 drugs are a dominant force in the pharmaceutical industry. Blockbuster products have generated tens of billions of dollars in annual revenue, driving market capitalization growth for leading manufacturers and influencing investor strategies across the sector. Their success has intensified competition, spurred mergers and acquisitions, and redirected research and development funding toward metabolic and obesity-related pipelines. Availability of generic versions broadens the revenue potential and improves accessibility for patients.

Researchers are continuing to address important clinical and ethical considerations. Long-term safety data is still evolving, and gastrointestinal side effects, adherence challenges, and questions about lifelong use are undergoing evaluation. Additionally, the medicalization of obesity has sparked debate on how best to combine lifestyle approaches with medicinal intervention.

The impact of incretin-based therapeutics is likely to expand further. As innovation continues, incretin-based therapies may potentially redefine not only the pharmaceutical market but also global strategies for managing chronic disease and promoting human health.

Based on current analyst consensus and published forecasts, the global number of patients using incretin-based therapies is expected to grow dramatically over the next decade, driven by obesity, T2D, and expanding indications.

Best-Estimate of Global GLP-1/Incretin-Based Therapies Patient Market Size

Assumptions

Current Baseline (2025): ~20–25 Million Patients

- The market is currently constrained by manufacturing supply and limited reimbursement.
- Consumption is currently driven by Type 2 Diabetes Mellitus (T2DM) indications.

Medium-Term (2030): ~45–55 Million Patients

- Regional Dominance: The U.S. remains the primary market (~25–30M), followed by the Rest of World (~12–15M) and Europe (~8–10M).
- Growth Drivers: Expansion is fueled by broader obesity coverage, improved supply chains, and the launch of oral GLP-1 alternatives which improve patient convenience.

10-Year Outlook (2036): ~65–90 Million Patients

- Market Pivot: Obesity is projected to become the dominant therapeutic indication, though diabetes will still represent ~35 to 45% of treated patients.
- Scale: This represents a penetration of roughly 3–5% of the global adult population.

Analyst Benchmarks

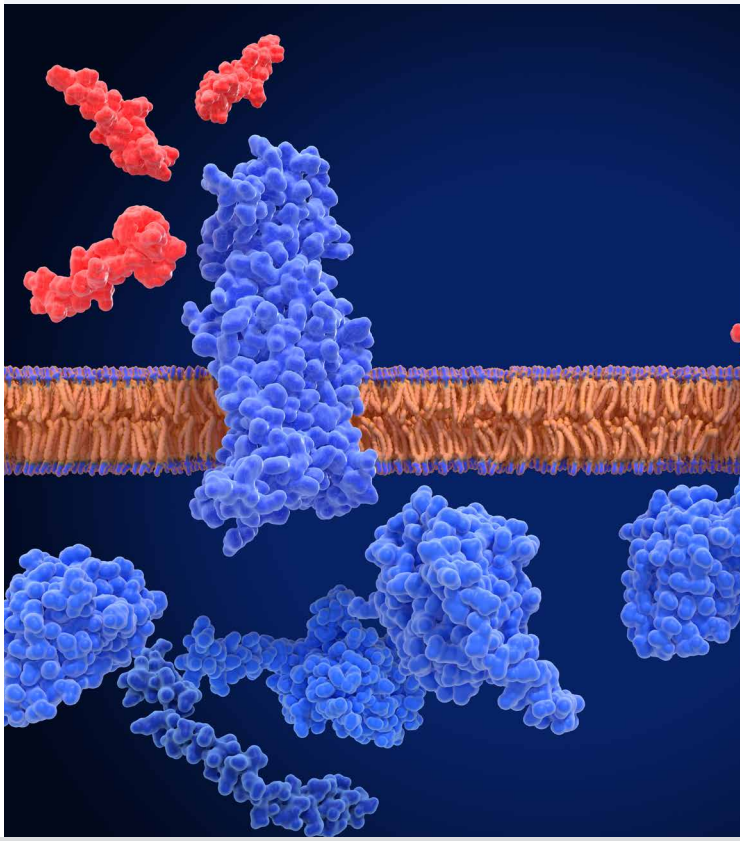
- UBS/McKinsey: High-end projections suggest up to 30 million patients in the U.S. alone by 2030. McKinsey & Company
- Morgan Stanley: Anticipates ~24 million U.S. users (7% of the population) by 2035. Definitive Healthcare
- TD Cowen: Notes that peak sales remain achievable even with relatively low global uptake (~2% of obesity patients), highlighting the massive, untapped potential. TD Securities

Why Early Development Strategy Matters

The global GLP-1/incretin-based therapy market is expected to expand from ~25 million patients today to roughly 65 to 90 million patients within the next decade, making it one of the largest chronic therapy classes in pharmaceutical history.

Patient numbers will ultimately depend on pricing, payer coverage, long-term safety data, and healthcare policy. If these therapies achieve widespread public reimbursement globally, patient counts could exceed the upper end of this range; if access remains restricted, growth may track closer to the lower bound.

As GLP-1 research expands into new mechanisms and indications, early-phase study design, biomarker selection, and patient characterization will play a critical role in generating the data needed to support smarter downstream decisions.



HOW ALTASCIENCES CAN HELP

The complexity of this therapeutic area demands the guidance and support of a CRO/CDMO partner with relevant experience, proven flexibility, and an integrated service offering that adapts to changing needs and endpoints in this fast-paced development area. As a pioneer in accelerated early-phase drug development, the team at Altasciences recognizes that the GLP-1 market is in a moment of transformation, evolving beyond its diabetes origins into a "golden era" of metabolic health. These therapies are now part of the therapeutic armamentarium for treating obesity and many of the associated comorbidities, including cardiovascular disease, chronic kidney disease, and emerging indications like neurodegenerative disorders.

GLP-1 and Metabolic Drug Development Expertise

- We have expertise in evaluating the complex pleiotropic effects of GLP-1 RAs while maintaining stringent standards for toxicological assessment and PK/PD modeling.
- We provide specialized support for intricate bioanalytical requirements including quantitative PK/PD analysis, immunogenicity profiling, and multiplexed biomarker assays optimized for GLP-1 therapeutics, next-generation co-agonists, and broader incretin-based modalities.
- We have a proven track record in metabolic disorders, including 50+ completed early-stage trials involving anti-diabetic and hypoglycemic agents such as insulin, GLP-1, SGLT-2, and DPP-4.
- We support industry-leading timelines with world-class development capacity across integrated nonclinical and clinical programs, supported by a strategic network of facilities throughout North America.

Large, Targeted Obesity and Metabolic Database and Site Network

Altasciences maintains a proprietary database of over 400,000 participants, with a proven track record of recruiting thousands of volunteers since 2016, including participants for some of the earliest GLP-1 studies:

- **35,000+** individuals with obesity (BMI >30)
- **10,000+** individuals with morbid obesity (BMI >40)
- **20,000+** individuals with metabolic syndrome
- **1,500+** patients with Type 2 Diabetes
- **750+** patients with Type 1 Diabetes

We have access to participants with MASH/NASH/NAFLD and other obesity-related co-morbidities via an expansive North American site network focused on early-phase patient enrollment.

Why Partner With Us for GLP-1 Development

At Altasciences, we don't just support metabolic programs; we anticipate their evolving challenges. Our Acceleration Platform integrates nonclinical safety testing, bioanalysis, and Phase I/II clinical trials within a single organization, enabling faster timelines and a more efficient path to clinical proof-of-concept.

By helping sponsors swiftly navigate the complex pharmacological challenges of next-generation incretin-based therapies, Altasciences is supporting those that are pioneering the shift toward more accessible, needle-free oral options and potent combination therapies that will define the future of chronic disease management.

ALTASCIENCES' RESOURCES

Scientific Publications

The Altascientist Issue 42—Managing the Complexities of GLP-1 Drug Development

Poster—Leveraging Nonclinical Safety Evaluation Findings to Expedite Next-Generation Glucagon-like Peptide-1 Receptor Agonists (GLP-1RAs) Development for Metabolic Disorders and Beyond

Poster—GLP1-RA: Overcoming Known Pharmacological Effects

Case Study—GLP-1 RA: Rapid Clinical Phase I Study Execution

Article—The golden era of GLP-1 drugs: How will it impact medicine and society?

Fact Sheet

Clinical Obesity Trials and GLP-1 Programs

On-Demand Webinar

The Golden Era of GLP-1 Drugs

ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 30 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, clinical monitoring, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.