Insights Hub

Redefining Value in Obesity Drug Development:

A Focus on the Full Cardiometabolic Continuum

Syneos® Health

Introduction

GLP-1 receptor agonists have fundamentally changed the diabetes and obesity treatment landscape and are now demonstrating outcomes in multiple cardiovascular, kidney and metabolic (CKM) diseases, and even disease modification and prevention. This health advancement opens new worlds of opportunity for sponsors who can rise to the challenges of adopting a pathway-centric development strategy.

Increasingly, obesity is recognized not as an isolated condition but rather as a foundational component of a broader CKM continuum. Consequently, the focus of GLP-1 development is shifting from how much weight patients lose to how effectively therapies alter the progression and outcomes of multiple interconnected diseases. Indeed, some GLP-1s are also indicated for cardiovascular disease, chronic kidney disease (CKD) and sleep apnea in addition to weight reduction and glycemic control.

The next phase of obesity drug development will not be won by marginal differences in mean population weight loss. It will be won by assets that demonstrate credible modification of the biologic drivers of disease risk—adipose dysfunction, ectopic fat, inflammation, insulin resistance, hemodynamic stress, hepatic fibrosis, renal injury and sleep-disordered breathing—and that translate those effects into durable, organ-specific, patient-meaningful outcomes. In this future state, obesity is not a single endpoint but an entry point into specialized development pathways for cardiovascular, renal, hepatic, metabolic, respiratory and functional disease.

Thus, obesity has evolved from a therapeutic endpoint to a therapeutic gateway, presenting sponsors with vast market potential. To seize the opportunity, sponsors will need to adopt a fundamentally new development strategy: They must focus not on developing drugs for a single indication but rather on demonstrating value across the full CKM continuum. This will require creating and executing a more programmatic, integrated strategy across multiple functions and phases of development. More will be expected of early-phase planning, and biomarker development will be even more critical. Trial designs must accommodate greater complexity and include decentralized components. The endpoint strategy will need to be broader and draw upon real world evidence (RWE).

The remainder of this paper explores the implications of this shift in how obesity is viewed and the strategies needed for sponsors to succeed in this rapidly evolving landscape.

Weight Loss Is Becoming Commoditized

The weight-loss market is a major area of opportunity for the pharmaceutical industry, given widespread and longstanding unmet need. Obesity has been considered an epidemic in the US for at least two decades, and today nearly a third of US adults are overweight and 42.4% are obese.[1] The prospects for continued growth in the anti-obesity market have increased substantially with the availability of more patient-friendly oral formulations of GLP-1s, new coverage by Medicare and international adoption.[2] By 2033, the global market for GLP-1 receptor agonists is predicted to reach USD $185.3 billion at a CAGR of 12.4%.[3] By 2035, it is estimated that 30% of those in the US who are obese or diabetic will be treated with GLP-1 therapies, as will 10% of those in the rest of the world.[2]

Innovation in this area is strong, with researchers making advances in engineering peptides, improving efficacy, reducing dose frequency, developing oral formulations and exploring combination products.[3] Currently, a number of incretins are in late-stage development, including oral formulations and triple agonist medications that target three hormone receptors. Of particular note is retratrutide (an investigational drug), Eli Lilly's triple agonist, which is showing up to 30.3% weight loss at 104 weeks. A number of developers are also working on non-incretin adjuncts (such as amylin, NLRPs, GDF15, INHBE and NEK7) that enhance and broaden the efficacy of weight loss drugs while targeting other metabolic systems.

Thus, GLP-1s are fast becoming the backbone, or therapeutic platform, of a number of therapies that address the comorbidities of obesity, and their importance to the industry and to population health is immense. Anti-obesity drugs are no longer just about weight loss but about organ protection and potentially about reduced morbidity and mortality.

Inevitably, though, this investment in weight-loss therapies will result in a crowded market, creating a differentiation crisis. The next differentiator may be less about peak weight loss than sustained disease control. Obesity is chronic and relapsing, and discontinuation of therapy can lead to weight regain and reversal of cardiometabolic improvements. Development programs should therefore test maintenance strategies, dose flexibility, tolerability over time, relapse prevention and durability of organ-specific benefit—not simply maximal weight reduction at a fixed time point.

Obesity Is Recognized as a Driver of CKM Disease

These changes in the development landscape are the result of an emerging understanding of obesity as both a complex chronic disease and as a pathophysiologic driver of cardiometabolic disease.[4]

The Eastern and Southern Europe Diabetes and Obesity Expert Group explains the connection: "As adipose tissue expands and becomes dysfunctional, it contributes directly to insulin resistance, chronic inflammation, altered lipid metabolism and other pathophysiologic processes that drive conditions such as type 2 diabetes, cardiovascular disease, metabolic dysfunction-associated steatohepatitis (MASH), chronic kidney disease and heart failure. In this sense, obesity is not merely a risk factor associated with these conditions; it is often a causal disease process that contributes to their development and progression."[5]

The American Heart Association has created a CKM health framework that positions cardiometabolic disease as a staged, multisystem disorder shaped by the interplay among metabolic risk factors, chronic liver disease, kidney disease and the cardiovascular system.[6] Relatedly, the American Diabetes Association in its *Standards of Care in Diabetes* states: "Obesity is a key pathophysiologic driver of diabetes, other cardiovascular risk factors (e.g., hypertension, hyperlipidemia, metabolic dysfunction-associated steatotic liver disease (MASLD) and inflammatory state), and ultimately, cardiovascular and kidney disease."[7]

Weight loss is now seen as an early intervention to prevent other CKM disorders and, consequently, to extend longevity. However, the continuum should not be interpreted as a single homogeneous pathway. Obesity-related complications differ in biology, natural history, clinical burden and evidence requirements. A cardiovascular program must prove event reduction or cardiac-functional benefit; a MASH program must address steatohepatitis, fibrosis and liver outcomes; a renal program must show effects on albuminuria, eGFR slope, kidney failure or renal events; an obstructive sleep apnea (OSA) program must show improvements in apnea-hypopnea index, hypoxic burden, symptoms and functional sleep outcomes. Treating obesity as a driver of disease therefore requires specialization—not merely adding comorbidities to a weight-loss trial.

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Regulators Support a Pathway-Centric Approach

Regulatory guidance is beginning to reflect the same shift seen in the science of obesity.

In January 2025, the US Food and Drug Administration (FDA) issued a new draft guidance, *Obesity and Overweight: Developing Drugs and Biological Products for Weight Reduction*, replacing its much older 2007 draft guidance. The update reflects how much both the science and development landscape have changed.[8]

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The guidance is limited to studies assessing the effectiveness of drugs to reduce weight, and so weight loss remains a primary efficacy measure. Yet, even in this context, the guidance places greater emphasis on:

- Obesity as a chronic disease
- Long-term treatment and maintenance
- Assessment of obesity-related comorbidities
- Patient-centered outcomes and function
- Broader benefit-risk considerations beyond weight alone

Clinical strategy, operational design, RWE generation and value demonstration need to be coordinated from the outset to reduce lifecycle risk.

The FDA's approval of semaglutide injection to reduce the risk of serious cardiovascular events[9] as well as its updated obesity drug development guidance signal a recognition that obesity therapies may offer value well beyond weight reduction. In fact, the agency "encourages assessment of the effect of drugs on the manifestations of obesity or overweight beyond excess adiposity."[8] For sponsors, this expands the market opportunity while also increasing the challenges of clinical development, most particularly in creating endpoint and evidence-generation strategies.

Weight Loss Is Becoming Table Stakes for GLP-1s

Clinicians already have multiple options for treating obesity, and the available choices will increase markedly in the next five years; the market will soon be flooded with multi-agonists targeting obesity. Simultaneously, we are reaching a "point of diminishing returns for raw weight loss percentages" as studies suggest Eli Lilly's retatrutide will induce "more weight loss than most… patients will ever clinically require."[11]

Under these conditions, weight loss will become the baseline expectation for GLP-1s. Beyond that, efficacy will be assessed based on how the weight is lost and over what period of time, patient persistence and adherence on medication, maintenance of weight loss, and how well an obesity treatment manages select downstream diseases.

The more important competitive question will be whether an asset can demonstrate disease modification in the complications that matter most to patients, clinicians, payers and regulators: fewer cardiovascular events, slowed kidney or liver progression, improved glycemic durability, reduced OSA severity, preserved function and sustained benefit after initial weight loss.

In light of the growing and inevitable nuances among the options, clinicians can apply an individualized approach to treating patients with obesity or those who are overweight. Prescribers will be able to match the molecule to the specific patient given the patient's phenotype, body mass index, other metabolic conditions, ability to tolerate side effects and risk of muscle loss. Providers will be able to fine-tune their treatment approach with GLP-1 receptor agonists in the ideal combination ratio and at the appropriate dose, patient by patient.

Sponsors Must Revamp Their Development Strategies

Traditionally, sponsors have segmented their clinical development strategies for cardiometabolic disease, defined patient populations narrowly and focused on singular endpoints. However, to meet the demand for products that both treat obesity and target downstream metabolic diseases, sponsors will need to adopt a more integrated model of clinical development. In this new environment, they will need to think more holistically and adopt a pathway-centric strategy. They must consider how interventions to treat obesity influence multiple aspects of cardiometabolic disease prevention and progression and how those effects translate into long-term outcomes. To do otherwise could mean missing how risks and benefits alike accumulate across systems.

Pursuing a pathway-centric strategy rather than isolated programs has significant implications for all phases of development and requires earlier and closer alignment across functions. Clinical strategy, operational design, RWE generation and value demonstration need to be coordinated from the outset to reduce lifecycle risk. In particular, we recommend that sponsors consider five key areas to design trials around disease pathways.

ADDRESS MARKET REALITIES IN EARLY-PHASE PLANNING

In general, decisions made in early development about populations, endpoints, comparators and data collection will now have even greater implications for regulatory approval, market access and early clinical adoption. Therefore, in phase I, sponsors must not only establish safety but also surface cardio-renal and other metabolic signals that clarify the compound's biologic fit along the disease continuum. This will both reduce downstream risk and identify additional potential indications.

Sponsors should map early signals to potential development pathways—atherothrombotic risk, heart failure biology, renal injury, hepatic inflammation/fibrosis, glycemic progression, sleep-disordered breathing, body composition or physical function—and then design the evidence package around the most credible pathway rather than around weight loss alone.

Multimorbidity affects recruitment, stratification, background therapy, safety monitoring, protocol burden, endpoint adjudication and missing data. Protocols must therefore predefine background-care standards, rescue algorithms, safety monitoring, adjudication processes and strategies to retain participants after treatment interruption so that long-term outcomes remain interpretable.

Sponsors will need to consider a number of real-world clinical and commercial factors (such as future unmet need and potential areas of differentiation) from the early phases of development in order to strengthen their narrative for regulators and payers. This requisite is particularly relevant for emerging biotechs looking to strengthen their case for investors.

The shift to regarding obesity as a therapeutic gateway will require that sponsors differentiate their market entries in ways that extend beyond the sheer amount of weight that can be lost. Opportunities for differentiation that should be considered from early-stage development include:

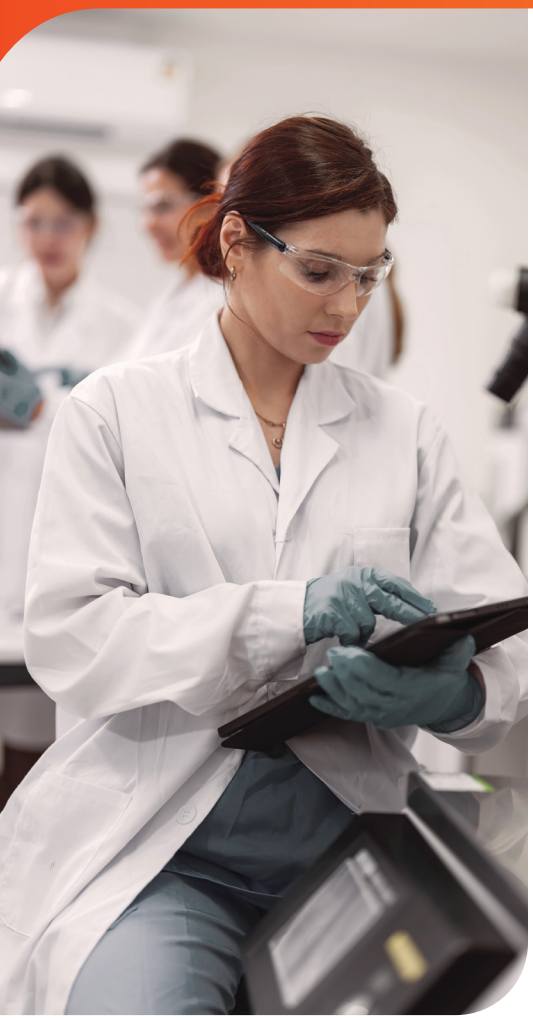
Incorporating patient convenience factors such as streamlined delivery mechanisms and flexible dosing schedules (e.g., rapid improvements in the efficacy of once-a-day pills are aiming to negate the efficacy advantage of injectables).

Utilizing efficacy factors such as longer-acting molecules to significantly reduce injection frequency, the quality of the weight loss and the preservation of lean muscle.

Combining multiple agonists to target other cardiometabolic conditions in support of personalized treatment approaches.

Integrating the treatment with digital health solutions. The FDA recommends that investigational obesity drugs be used in addition to lifestyle management programs, which are prime applications for digital health tools.[8]

Differentiating based on the disease pathway. Identify the complication phenotype in which the asset has the strongest biologic rationale and highest value potential—e.g., ASCVD risk reduction, HFpEF symptom/function improvement, MASH fibrosis improvement, CKD progression slowing, glycemic durability, OSA severity reduction or preservation of physical function—and design early biomarker and endpoint collection to support that pathway.



STRENGTHEN BIOMARKER DEVELOPMENT

Eligibility for trials of obesity drugs that also target downstream diseases will be determined by biomarkers. AI can be useful in identifying and recruiting patients with specific characteristics, and this precision in patient selection will be increasingly important to support the practice of personalized treatment in clinical practice.

Biomarkers should be used to move development from weight-response measurement to disease-risk biology. In early development, sponsors should define which biomarkers establish biologic fit, which enrich for patients most likely to benefit, which can serve as early indicators of disease modification, and which monitor safety in vulnerable multimorbid populations. Across the CKM continuum, this may include inflammatory markers, glycemic measures, visceral or ectopic fat imaging, cardiac biomarkers and imaging, UACR/eGFR for renal injury and progression, liver stiffness or fat/fibrosis measures for MASLD/MASH and sleep-specific measures such as AHI or hypoxic burden when OSA is the target complication.

Novel biomarkers are evolving from exploratory research tools into strategic assets across the obesity drug development lifecycle. Sponsors that effectively integrate validated biomarkers into phase I–III programs can improve patient selection, demonstrate biological proof of concept, support regulatory and payer discussions, and differentiate their therapies in a highly competitive market. As obesity increasingly intersects with cardiovascular disease, MASH, CKD and other cardiometabolic conditions, biomarker-driven development is likely to become a defining feature of next-generation obesity clinical trials.

CONSIDER PLATFORM TRIAL DESIGNS TO ACCOMMODATE STUDY COMPLEXITY

Clinical trials will become vastly more complex as the focus shifts from treating singular diseases, populations and endpoints to a more pathway-centric view that considers how interventions influence multiple aspects of cardiometabolic disease prevention and progression, and how those effects translate into long-term outcomes. This holistic view mirrors the real-world experience of patients being treated for obesity; typically, clinicians do not manage obesity in a silo, but rather alongside multimorbidity, polypharmacy and long-term health consequences.

Platform trial designs are an efficient way to handle the complexity of testing various combinations of drugs across multiple obesity-related indications or comorbidities. The FDA has recently released revised draft guidance on the design and analysis of trials conducted under a master protocol, stating, "Master protocols can reduce duplicative infrastructure, streamline data collection, and accelerate the generation of evidence needed to support regulatory decision-making."[10]

These trials are also destined to be large. For weight-reduction trials alone, the FDA recommends having 3,000 subjects randomized to the investigational drug and at least 1,500 randomized to the placebo. It will, therefore, be common for phase III trials of multi-agonist drugs to enroll 4,000 to 6,200 patients.

RWE will be essential to devising an effective evidence generation strategy that focuses on the patient populations actually being treated—people with multiple conditions, complex medication regimens and care pathways that do not fit neatly into trial assumptions. In practice, these real-world insights inform how standard of care treatments are sequenced and where traditional design assumptions are most likely to break down.

No discussion of cardiometabolic disease is complete without acknowledging the role of social determinants of health (SDOH). Factors such as income, education, access to care and environmental conditions affect who enrolls in trials, how well participants adhere to protocols, and whether study findings translate into real-world effectiveness. Failing to account for SDOH in the trial population is both a missed opportunity for advancing health equity and a source of scientific and commercial risk.

FIND TRIAL EFFICIENCIES THROUGH DECENTRALIZATION

If we think about the complications of having subjects with comorbidities in a trial, multimorbidity affects recruitment, stratification, background therapy, safety monitoring, protocol burden, endpoint adjudication and missing data. Protocols must therefore predefine background-care standards, rescue algorithms, safety monitoring, adjudication processes and strategies to retain participants after treatment interruption so that long-term outcomes remain interpretable.

Trials of this size will require a decentralized infrastructure. Common approaches to managing these large, complex trials include hybrid trial designs that combine site and home visits, collecting data from wearables, making use of remote biosampling, relying on natural history controls and following pragmatic protocols that require limited laboratory tests for safety surveillance. These patient-friendly solutions will help with recruitment and retention over long-duration trials (testing for 76-104 weeks is now standard.)

ADOPT A BROADER SET OF ENDPOINTS

Starting in the early stages of development, there is a need to move beyond single-disease endpoints and integrate cardiovascular, hepatic, renal and metabolic endpoints—as appropriate for the envisioned indication—into the evidence generation plan. Strategies that continue to center on single endpoints or narrowly defined populations can increase uncertainty and development risk as well as severely limit an asset's potential. Trials that are too narrowly focused may generate evidence that lacks relevance once the therapy enters clinical practice.

Outcomes-based endpoints could include MACE-4 hard endpoints (coronary heart disease death, myocardial infarction, stroke and revascularization), renal outcomes, heart failure, hospitalizations, etc., and can be used for value demonstration. Relatedly, research should answer the question: "How much weight loss is clinically necessary to achieve metabolic remission or address comorbidities?"

With respect to weight loss, regulators mandate measures of body composition from simple waist-to-height ratios to DXA/MRIs in order to support quality of weight loss claims. Other obesity endpoints could include muscle sparing/visceral fat endpoints measured via MRI.

RWE can be used to demonstrate to payers and health technology assessment bodies the durability of benefit and impact on disease progression.

Conclusion

Given the pace of progress in obesity research and the new framing of obesity as a therapeutic gateway to other cardiometabolic diseases, sponsors must anticipate where clinical practice is headed and then let the science lead. In this new therapeutic landscape, treatments that demonstrate benefits across multiple domains or that address upstream drivers of disease will be better positioned to meet future standards of care and value expectations.

Winning in obesity-drug development will depend on the ability to manage the complexity of multiple, interconnected conditions and to make deliberate choices that reflect the realities of science, care delivery and patient journeys—in other words, on the ability to design for the full cardiometabolic reality.

The competitive question in the future will be not "how much weight" but "which disease biology, which patient, which endpoint and how durable is the benefit."

Recognizing obesity as a therapeutic gateway will have profound implications for sponsors' development strategies and market potential and, ultimately, for population health.

CONTRIBUTORS

Anup Sabharwal, MD MBA FACC FACE FESC FAHA FASPC FNLA
Head of Research & Development, Cardiovascular-Kidney-Metabolic, Syneos Health

James Snyder, MD
Medical Strategist, Medical Management, Cardiovascular-Kidney-Metabolic, Syneos Health

Tristan Baldwinson
Therapeutic Area Head, Cardiovascular-Kidney-Metabolic, Syneos Health

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Contact us
Syneos Health
1030 Sync Street
Morrisville, NC 27560
Phone: +1 919 876 9300