ARTICLE

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Beyond weight loss: Addressing critical unmet needs in obesity treatment



A KEY QUESTION How can sponsors develop obesity therapies that deliver benefits beyond weight loss?

KEYWORDS Cardiometabolic Clinical Trials, Patient Recruitment Strategy, Site Selection and Engagement, Patient Retention, Clinical Trial Enrollment, Clinical Trial Execution

The emergence of highly effective anti-obesity medications (AOMs) has transformed treatment, producing levels of weight loss previously difficult to achieve with medication. Yet current therapies still face challenges with tolerance, adherence, access and patient burden, among many others.

To help drug development sponsors better understand these issues, this white paper examines:

- Today's evolving obesity landscape
- The importance of maintaining high-quality weight loss
- Opportunities for drug development sponsors
- Future considerations for developing more tolerable, patient-centered therapies

A chronic condition without a simple cure

Like many other chronic diseases, obesity requires long-term treatment. However, access and reimbursement are still limited[1] and data suggests that more than 50% of patients discontinue GLP-1 treatment after one year.[2]

As expected, discontinuation of AOM treatment after achieving initial weight loss is associated with weight regain, as observed in a Phase III randomized withdrawal study (SURMOUNT-4) of participants who discontinued tirzepatide.[3]

Sponsors must understand how to manage patients' expectations, develop more affordable, better-tolerated treatments and help drive acceptance of long-term therapy to close the gap on unmet need.

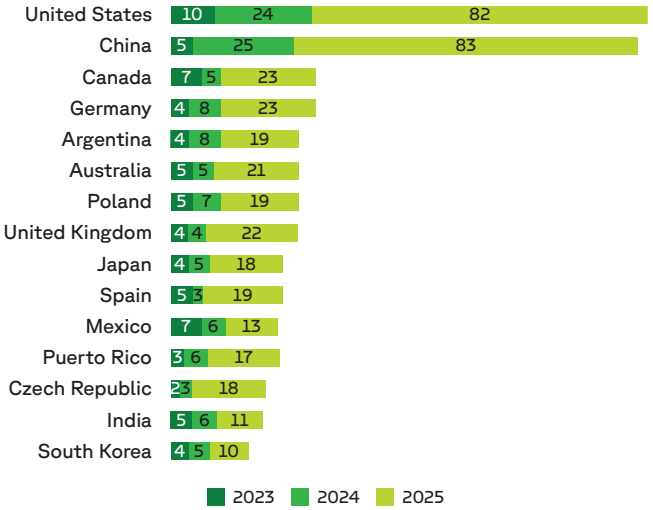
Examining an evolving obesity landscape

Historically, approaches to obesity management have focused on lifestyle modification, older pharmacologic therapies and metabolic or bariatric surgery.[4] However, sustained substantial weight loss can be difficult because biological mechanisms actively resist it through coordinated physiological adaptations. Surgery can produce substantial, long-lasting weight loss, but it is invasive and not appropriate or accessible for every patient.[5]

The development of GLP-1 receptor agonists has represented a major therapeutic advance. Semaglutide demonstrated approximately 15% average weight loss in major obesity trials, while tirzepatide, which targets both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), has produced mean weight loss exceeding 20% at higher doses in clinical trials.[6]

The field is now moving toward therapies that activate multiple complementary biological pathways, with the U.S. and China as the leading contributors.

 # Obesity trials by phase by year (all status)



Obesity trials by trial country by year (only ongoing trials) | Top 15 countries

Emerging therapies include dual and triple agonists, amylin-based therapies, oral GLP-1 receptor agonists and combinations designed to improve efficacy, tolerability or body composition. This development reflects the growing recognition that obesity cannot be adequately addressed through a single biological pathway.[7]

The shift from weight management to health improvement

Obesity is associated with a broad range of comorbidities, including Type 2 diabetes, cardiovascular disease, metabolic dysfunction–associated steatotic liver disease (MASLD), certain cancers, chronic kidney disease and autoimmune diseases, contributing substantially to morbidity and mortality.[8]

Cardiovascular disease is a particular focus of obesity therapy as it is considered the leading cause of obesity-related morbidity and mortality.[9] Semaglutide has demonstrated cardiovascular benefit in people with overweight or obesity and established cardiovascular disease, showing that an anti-obesity medication can provide benefits extending beyond weight reduction.[10]

Because these medications can play an important role in addressing many medical conditions, drug development sponsors must also focus on durable health improvements through a sustained disease management paradigm.[11]

Driving long-term success in obesity treatment

The long-term success of anti-obesity medicines will depend, among other factors, on maintaining high-quality weight loss while preserving healthy body composition and protecting skeletal muscle and bone mass.

Next-generation treatments should aim to offer complementary mechanisms of action beyond appetite suppression, while providing good tolerability and a convenient dosing regimen, improving associated comorbidities and preserving health and physical function during weight reduction. Drug development sponsors should take account of the following considerations:

Regaining weight remains a persistent challenge

After weight loss, individuals experience metabolic adaptation, including reduced energy expenditure and compensatory neurohormonal responses that increase appetite and promote regain.[12]

These mechanisms help explain why maintaining substantial weight loss through lifestyle intervention alone can be difficult.

Fat distribution matters

BMI remains a useful screening measure, but it does not distinguish fat mass from lean mass or capture fat distribution.

Two individuals with identical BMI can have substantially different visceral adiposity, muscle mass, metabolic risk and physical function.[13] Assessment of body composition provides information not captured by body weight alone.

Losing fat while preserving skeletal muscle mass and function and bone mass

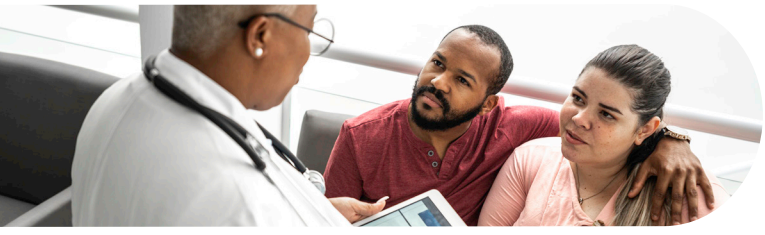
Weight reduction can involve decreases in both fat and lean mass, making the quality of weight loss as important as its magnitude.

Adequate intake of high-quality protein is critical for supporting muscle preservation during weight reduction.

Opportunities for anti-obesity therapies

While weight loss efficacy has advanced dramatically, future anti-obesity therapies need to address:

- **Tolerability and adherence:** Gastrointestinal (GI) adverse events remain common, with 70–90% of patients reporting at least one GI event in clinical trials,[14] which can affect willingness or ability to continue treatment



- **Cost, access and availability:** High costs, limited insurance coverage, complex prior-authorization requirements and periodic medication shortages can substantially restrict access to anti-obesity medications, particularly newer GLP-1–based therapies[15]
- **Patient burden:** Treatment characteristics such as injection frequency, food or water restrictions and storage requirements can affect patient preferences.[16] Oral formulations could eliminate injections and potentially simplify treatment
- **Durability:** Because weight regain is driven partly by persistent biological adaptations, stopping therapy without an alternative maintenance strategy is inherently difficult. Potential solutions include exploring long-term treatment, less frequent dosing, sequential therapies and combinations targeting complementary pathways

Looking ahead to the future of obesity treatment

The obesity treatment pipeline is becoming increasingly diverse as sponsors look to move beyond inducing weight loss toward long-term disease management. Future treatments may also become more personalized based on several factors such as obesity phenotype, comorbidities, previous treatment response, body composition and metabolic risk.

Success will be determined by several factors, such as:

- How long weight loss is maintained
- Changes in body composition, cardiometabolic health and physical function
- Long-term health outcomes

Real-world evidence will be equally important for understanding how treatments work and are maintained across people with different health conditions, socioeconomic circumstances and access to care. Ultimately, future therapies will be evaluated by how well they maintain weight loss benefits while balancing tolerability, durability, convenience, affordability and improved obesity-related health outcomes over time.

Want to learn more?

Get more information about our obesity treatments at fortrea.com

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AR_0030_Obesity Treatment_1026