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Anti-obesity drug development: advances, challenges and mitigations to maximize success

Contributors

Peter Alfinito, PhD, Executive Director, Internal Medicine

Claudia Filozof, MD, PhD, Vice President, Therapeutic Area Head of Obesity, MASH and Hepatology Indications

Obesity is one of the most common health conditions across the world and has become the most broadly impactful health factor of our time.[1] Given the magnitude of the problem and its growth trajectory, options for patients to improve their health have been sought for many years.

The historical development of anti-obesity treatments has been difficult with several periods of excitement and optimism followed by frustration and failure. Some drugs never reached the market and others were withdrawn early due to unacceptable side effects. Phentermine and diethylpropion represented some of the first attempts in the 1950s and 60s to reduce weight but cardiovascular risks and abuse potential led to their demise in the 1970s. The next generation of drugs, fenfluramine and dexfenfluramine, were in the EU market since the 1980s. However, only a few years after they were approved by the FDA in 1990, evidence of superior efficacy of the combination with phentermine was published, which led to the widespread use in the U.S. of a combined treatment. A few years later, reports of cardiac valvulopathy led the manufacturer to withdraw fenfluramine and dexfenfluramine from the market. Other drugs, such as sibutramine and rimonabant, have also been withdrawn due to safety concerns.[2]

Recently, a better understanding of the role of the entero-pancreatic hormones in the regulation of appetite and energy homeostasis has led to the identification of numerous targets for potential anti-obesity drug development. This included signals from the gut, (e.g., cholecystokinin (CCK), ghrelin, glucagon-like peptide-1 (GLP-1), gastric inhibitory peptide (GIP), peptide YY (PYY)), pancreas (e.g., insulin, amylin, pancreatic polypeptide) and adipose tissue (e.g., leptin, adiponectin). In December 2014, after more than 10 years in the market for T2DM indication, Liraglutide was the first GLP-1 agonist approved for an obesity indication; most recently, Semaglutide was approved followed last year by Tirzetapide, a dual GLP-1/GIP agonist.[2,3]

Navigating the rapidly growing anti-obesity drug development landscape

We have seen the approval of the GLP-1 class of drugs that offer acceptable, safety and tolerability profiles with weight loss from dual agonists reaching a double-digit drop. With these compounds now available in some markets, a once wide-open field has become very competitive. Here, strategic trial design and conduct are essential to launch the next generation of pharmacological treatments for obesity.

The success and potential of the GLP-1-related mode of action, as well as other incretins, has changed the perception of the probability of success in developing a pharmacological treatment for obesity. With this change, the field has expanded dramatically with six ongoing marketing authorization trials,[4] more than 200 companies currently engaging in clinical trials and another 100 companies in preclinical development.

The objective of the next generation of anti-obesity drugs is not only to achieve long-term weight loss and maintenance but to also target specific reduction in fat mass with preservation in lean body mass. Multiple sponsors are now exploring different compounds with complementary/synergistic modes of action to the available GLP-1 agonists to reach these objectives. Additionally, providing beneficial effects on comorbidities will be an important component of anti-obesity compounds. Given that patients will be enrolled with cardiovascular, metabolic and renal comorbidities, the trial design must address multiple factors related to these conditions within the umbrella of obesity.

While the availability of patients is not the issue in obesity trials, site availability, interest and resourcing start to become issues in a competitive landscape. In addition, site budgets begin to increase as sponsors seek to have their trial placed at the top of the list and the mechanism of action, proof of principle and science around a sponsor's drug become decision points for site engagement. The next generation of clinical trials will need to contend with these changes, invoking tactics that specifically address the competitive landscape by introducing new sites and networks, involving more centers outside of the United States, paying higher grant fees and developing communication and publication strategies to ensure their compound is well-known in the field.

The next generation of obesity trials will also need to think carefully about patient and site burden in their protocol design so they stand out as the most attractive studies to join. Sponsors will need to decide whether to employ a placebo versus an active controlled study design and whether to include an open-label extension, both of which have implications for operational conduct, timelines and cost.

Finally, the next generation of clinical trials in obesity must account for patient diversity. Historically, enrollment in obesity trials was "first-come, first-served" basis, leading to rapid enrollment of high patient numbers and low diversity. With the 2022 FDA guidance, however, comes the expectation that all pivotal clinical trials will have a Diversity Action Plan (DAP). This change will certainly impact trial design and conduct for obesity trials. Sites will have to be capped on gender and race with targets set to include historically underrepresented populations. The result could be slower and more expensive studies with higher site numbers. Careful feasibility, proper site selection and pre-identifying patients may be some of the ways to minimize the impact of FDA's DAP requirements. Supporting sites with dieticians who match the sites' patient population may be required to ensure patients remain engaged and compliant while bespoke advertising campaigns should be designed to reach specific patient populations.

Looking ahead to the new generation of anti-obesity compounds

There is no doubt a new era in obesity care is starting. Semaglutide, approved in 2021, and Tirzetapide, the first dual agonist approved in 2023, are leading to double-digit weight loss with an acceptable safety profile for the first time in the history of anti-obesity drug therapies. Multiple other molecules (including combinations of *entero*-pancreatic hormones and oral GLP-1 receptor agonists) are in late phase clinical trials, leading to weight loss comparable to bariatric surgery.[5] The new generation of anti-obesity compounds will lead to 15-25% or more weight loss at 1 year through the synergistic effects of compounds with different modes of action. Quality of weight loss (selective fat loss with preservation of lean body mass) and long-term weight maintenance are the immediate next objectives. The availability of all these compounds in the market will bring a challenge in compliance in placebo-controlled trials. Flexibility to maintain patients on standard-of-care therapy and/or open-label extension studies can help minimize drop-out rates.

Foreseeing these changes and being prepared to proactively address them is the key to seamlessly delivering new options to patients. Fortrea is at the forefront of obesity research, and we are ready to maximize the value of your asset in a rapidly changing environment.

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