Editorial

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First in class, best in class or a wild card: who will dominate the anti-obesity medication market?

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The anti-obesity medication (AOM) market presents a significant opportunity for pharmaceutical companies, with the global prevalence of obesity estimated to reach 1.9 billion by 2035. This review examines the unique characteristics of the AOM market and evaluates whether the principles of 'first-in-class' or 'best-in-class' are likely to determine market success. We argue that the multifactorial nature of obesity and the rapidly evolving AOM market necessitate a more nuanced approach. Factors such as weight loss efficacy, impact on obesity-related complications, mode of administration, patient access through reimbursement and strategic positioning will play crucial roles in determining the success of AOMs. While Novo Nordisk and Eli Lilly currently lead the race with their GLP-1 agonists, the competitive landscape is expanding with numerous drug candidates in the pipeline. We conclude that pharmaceutical companies must carefully consider their strategies, balancing clinical efficacy, patient preferences and market access to unlock the full potential of the AOM market. Ultimately, the winner will likely be determined by a combination of factors rather than a single 'first-in-class' or 'best-in-class' approach.

Obesity & the need for interventions

Obesity, and the multimorbidity commonly associated with it, is one of the most pressing challenges facing healthcare systems and wider society today. This makes the AOM market a significant commercial opportunity for pharmaceutical companies. The global prevalence of obesity, defined as BMI $\geq$30, was estimated to be 14% [1] (nearly 1 billion people) in 2020 with predictions that obesity prevalence could reach 24% (1.9 billion) by 2035 [1]. The resulting global economic impact is equally striking at US$1.96 trillion in 2020, rising to over US$4 trillion in 2035 [1] (considering the cost of treating obesity and its consequences, impact on economic productivity and premature retirement or death) and demonstrates the undeniable importance of obesity from a public health perspective.

The underlying etiology of obesity is multifactorial with contribution from poor diet, physical inactivity and other environmental factors. Not only does obesity have direct medical implications, it is also associated with an increased risk of a variety of other conditions termed obesity related complications (ORCs), such as Type II diabetes mellitus (T2DM), cardiovascular disease (CVD), osteoarthritis, sleep apnoea and certain types of cancers [2]. The risks of developing and the prevalence of a selection of ORCs are shown in Figure 1 [3,4]. There is therefore a clear need for interventions to reduce rates of obesity, for the benefit of patient outcomes, health system sustainability and society at large. However, there is a significant challenge with respect to contention around the recognition of obesity as a disease or not, and the implications of this on both clinical guidelines and funding for the treatment of obesity. For example, under the German Social Code, obesity is not recognised as a disease and hence pharmacological treatments are not reimbursed [5].

Current treatments for obesity include lifestyle interventions (such as improved diet and increased physical activity), pharmacotherapy and bariatric surgery, with tailoring required for each patient. Despite the apparent

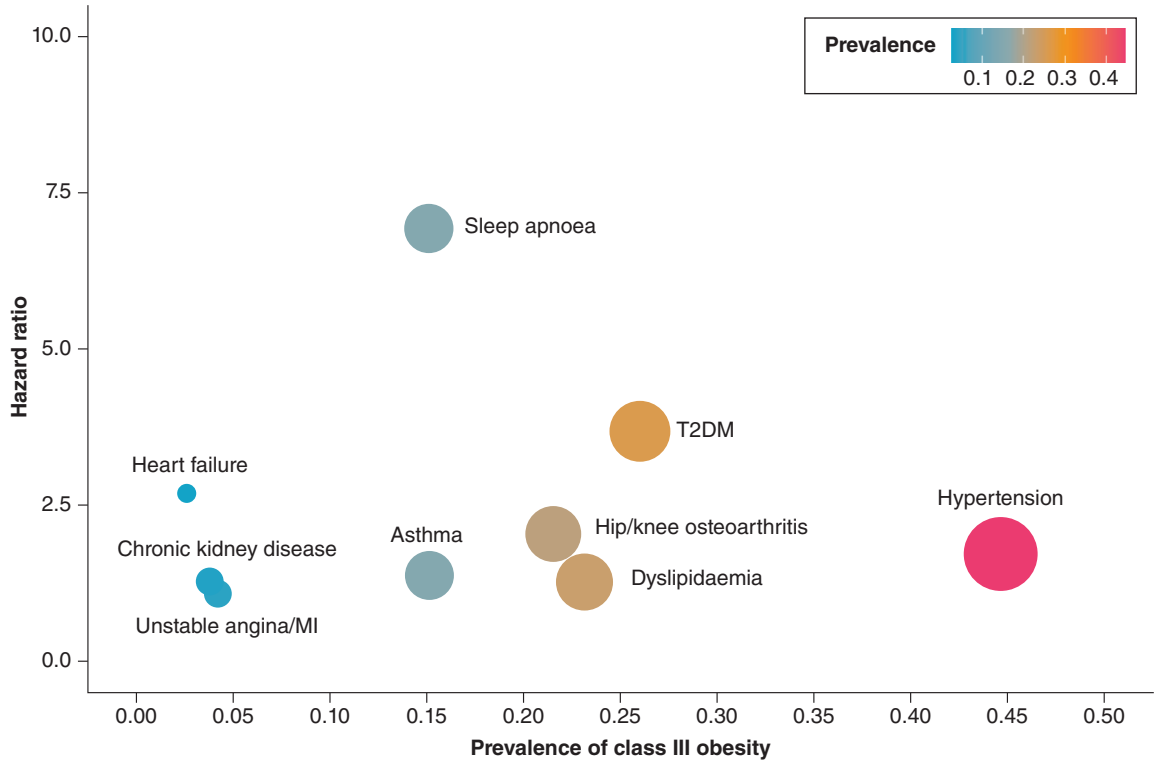

Figure 1. Hazard ratios for individuals with BMI of 45 kg/m^2 relative to a stable BMI of 30 kg/m^2 and prevalence of obesity related complications for individuals between BMI 40 kg/m^2 and 70 kg/m^2 (class III). Prevalence is shown as the proportion of participants in the study with the obesity related complication [3,4].
T2DM: Type 2 diabetes mellitus.

need for intervention, historically there have been few pharmacological treatment options available. However, it is a therapeutic area that is now experiencing strong innovation with the field recently being opened up by the glucagon-like peptide-1 (GLP-1) agonist class, and the rewards for the winner are staggering – analysis by Goldman Sachs estimates that the AOM market will grow to around $100 billion in 2030 [6]. As there are now a number of pharmaceutical companies vying to become the market leader in the AOM space, it begs the question of who will come out on top and how will they get there?

Best in class versus first in class

The common debate of whether 'first-in-class' or 'best-in-class' medications will gain the lion's share of a market is challenging to answer in the context of AOMs, given the market's unique characteristics: the scale of the eligible population, access challenges due to differing payer perception of obesity, and rapid innovation with newer treatment classes already entering the market. It is however an important debate to consider, given the impact it will have on the future drug development ecosystem, as well as clinical practice and patient outcomes. Drawing on our experience of obesity, market access and pharmaceutical commercial strategy, this review considers whether either of the first-in-class or best-in-class principles might apply to the AOM market, or if other factors are more likely to drive success.

A previous analysis has shown that first to-launch products are more and more likely to become the market leaders. For example, the RET kinase inhibitor selpercatinib (Retevmo; Eli Lilly), launched just 3 months before pralsetinib (Gavreto; Blueprint Medicines), has managed to obtain more than 70% market share in USA, and now has the entire ex-US market to itself given the withdrawal of pralsetinib from these markets [7,8]. Despite examples like these, market share can be won by having a best-in-class profile, differentiating on efficacy, safety or convenience. A well cited example of best-in-class being successful, when viewing 'best' from the perspective of the drug being the most clinically efficacious, is the treatment of raised LDL cholesterol with atorvastatin (Lipitor; Pfizer). It was the fifth statin that came to market but became the market leader (and highest grossing drug of all time) due to

its therapeutic advantage over statins launched before it. However, despite this being a widely cited example of best-in-class winning out, Pfizer also had other strategies to support the success of Lipitor including pricing lower than competitors and aggressive marketing (including direct to consumer marketing in USA) [9]. Similarly, other strategies besides increased efficacy have proved effective in the oncology therapeutic area, with clinical trial strategy determining success for pembrolizumab (Keytruda; Merck). Both pembrolizumab and nivolumab (Opdivo; Bristol Myers Squibb) are programmed death receptor-1 (PD-1) inhibitors that are used to treat many different types of cancers with similar levels of efficacy. Opdivo was the first PD-1 inhibitor in the world to receive regulatory approval, however Keytruda now outsells Opdivo by more than two to one. This was as a result of Bristol Myers Squibb taking a big risk by performing a randomized controlled trial in all patients for first-line treatment of the one of the largest cancer indications (non-small-cell lung cancer [NSCLC]), whereas Merck pursued a more cautious approach by focusing on a narrower segment of biomarker positive NSCLC patients [10]. The Bristol Myers Squibb clinical trial failed, whereas the Merck trial was successful, meaning Merck's strategic decision enabled to them to take the lead in NSCLC and ultimately Bristol Myers Squibb was never able to catch up.

The anti-obesity medication market

Taking a view of the AOM market, we believe that the concept of first-in-class winning does not necessarily hold, and believe the alternative avenues that pharmaceutical companies might take will become increasingly important. GLP-1 agonists are the only example currently where there are multiple AOMs within the same class approved for treating obesity. The first GLP-1 agonist on the market was liraglutide (Saxenda; Novo Nordisk), which had some success due to proven efficacy, however semaglutide (Wegovy; Novo Nordisk) then took the market by storm when it followed with even superior efficacy. Semaglutide was shown to facilitate a six-percentage point greater weight loss effect than liraglutide (13.8 vs 7.8%) [11]. More recently in November 2023, the US FDA approved tirzepatide (Zepbound; Eli Lilly) for chronic weight management (including weight reduction and maintenance) [12]. While tirzepatide is a GLP-1 agonist, it is also a glucose-dependent insulinotropic polypeptide (GIP) agonist, hence does not fit wholly into the same narrow definition of drug class as semaglutide/liraglutide but highlights the rapid innovation in the field. Further drugs in the pipeline utilizing novel treatment class combinations include: a combination of semaglutide and a long-acting amylin analog cagrilintide, called CagriSema (Novo Nordisk); and a triple agonist of GLP-1, GIP and glucagon receptors, called Retatrutide (Eli Lilly). We therefore consider AOMs broadly as treatments for obesity rather than focusing on a specific class. A summary of key current AOMs and upcoming AOMs are shown in Figure 2 [13–34].

What does best in class mean in the AOM market?

Given the multifactorial nature of obesity and the highly competitive, rapidly evolving AOM market, the factors that will determine which AOM is considered best-in-class are also likely to be complex. In the example above, it is already apparent that semaglutide won out over the first-in-class medicine, liraglutide, most likely due to its superior clinical efficacy in terms of weight loss, but there was also another advantage in terms of its once weekly administration as opposed to liraglutide's daily requirement [35]. In the AOM market, the best-in-class medication is likely to be determined by not only clinical efficacy in terms of weight reduction, but also in terms of weight maintenance, impact on ORCs and mode of administration.

Weight loss & maintenance

While there are likely to be multiple factors that determine what constitutes the best-in-class drug for AOMs, the focus for current AOMs is weight reduction. Current market leader Novo Nordisk's semaglutide showed a 14.9% weight reduction in the STEP-1 clinical trial in comparison to 2.4% reduction with the placebo at 68 weeks [36]. Meanwhile, ahead of its recent approval by the FDA, Eli Lilly's tirzepatide showed a 20.9% weight reduction at 72 weeks compared with 3.1% reduction with the placebo in the SURMOUNT-1 trial [37]. The phase IIIb clinical trial directly comparing both medications (SURMOUNT-5) is ongoing [38]. AOMs due to come to market in the future are likely to show incrementally improvements in weight reduction including Novo Nordisk's CagriSema and Eli Lilly's triple agonist retatrutide. However, it remains to be seen whether there will be a limit in how much weight reduction is clinically relevant or beneficial to patients. For a patient with BMI of 35, a weight reduction of approximately 29% will result in them achieving a BMI of less than 25, considered a healthy BMI. Furthermore, as there are fewer patients in the highest BMI categories, the market for AOMs with greater weight reduction becomes smaller; meanwhile high amounts of weight reduction may not be clinically appropriate for patients with only

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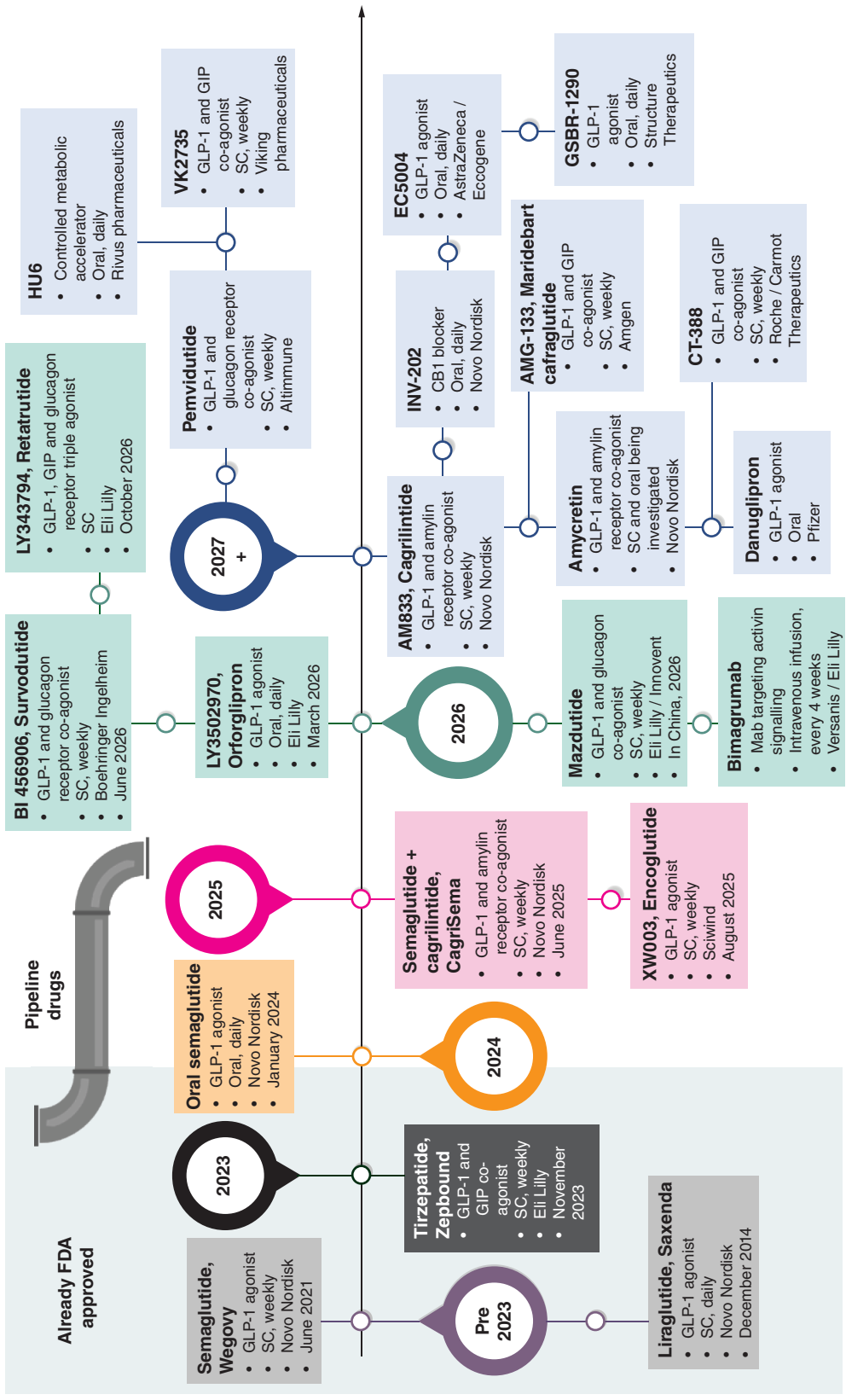

Figure 2. Current GLP-1 agonist anti-obesity medications and expected upcoming anti-obesity medications. Information from https://clinicaltrials.gov/ and/or company websites [13–34].
SC: Subcutaneaous.

moderately raised BMIs. Hence weight maintenance is likely to become an increasingly crucial factor in determining best in class AOM. When considering weight maintenance, recent AOMs such as semaglutide and tirzepatide have shown substantial weight regain after treatment cessation [39,40]. Additional longer-term data is crucial to assess these therapies after multiple years of continuous therapy and the effect of this on weight maintenance and complications relating to obesity. Having different dosing options (or different assets with varying degrees of efficacy) may give manufacturers an edge to potentially allow for dosing flexibility for weight maintenance.

It is not just about weight

In addition to weight loss and maintenance, the impact of novel AOMs on ORCs could be key to unlocking access to the obesity market. From a clinical perspective, it is important that AOMs not only lead to weight reduction, but that this in turn leads to improved patient clinical outcomes by reducing morbidity and mortality, while avoiding significant adverse effects. For example, while the risk of obstructive sleep apnea (OSA) is known to be higher in individuals with obesity (shown in Figure 1), it will be important to show that a reduction in weight with AOMs also leads to a reduction in OSA and its complications, such as hypertension and heart failure. Proving that AOMs improve ORC outcomes that are 'hard' and that have a significant cost to patients and healthcare systems (e.g., cardiovascular disease) will be critical for payers who are open to consider the benefits of therapeutics but need to be convinced of their value (especially if they apply a cost per quality-adjusted life year valuation framework) [41]. Alongside a weight loss benefit, demonstrating the extent of improvements in ORC outcomes could, in relevant markets, increase the likelihood of reimbursement or lead to better pricing for manufacturers.

Recently, the first clinical trial to show the benefit of AOMs in ORC outcomes was published; the SELECT trial looked at the impact of semaglutide on cardiovascular risk in patients with overweight and obesity. Results showed a 20% reduction in the risk of major adverse cardiovascular events including cardiovascular mortality [42]. Furthermore, semaglutide and tirzepatide are both in phase III trials investigating their benefits for several ORCs, including non-alcoholic steatohepatitis (NASH), OSA and osteoarthritis. Targeting ORCs with high unmet need, such as NASH will potentially be appealing to payers, clinicians and patients. However, trial design for these ORCs will be important for success. As potentially observed for semaglutide, treating NASH 'too late' may lead to a trial failure [43]. Companies will have to carefully plan elements of trial design, including who to treat, when to treat and end points to use to increase the likelihood of positive findings. However, excessive planning will also need to be balanced with speed to produce results before competitors. Trade-offs will need to be made based on stakeholder needs – does a company conduct a large trial for many years to achieve a payer gold standard of hard outcomes, or do they use surrogate end points? As noted for Keytruda, trial design can make or break a product.

The occurrence of adverse effects could also be a strong differentiator when it comes to patient preferences between similar efficacy drugs. While there is a list of possible side effects that can be experienced with the current AOMs on the market, in general they are well tolerated. However, fewer and more minor side effects can only support an AOM and will likely be another contributing factor to success as patients potentially need to take these medicines for a number of years.

Mode of administration

Another key differentiator that pharmaceutical companies could consider is the mode of administration. Patient preferences for the type of delivery (oral vs injectable), regularity of dosage (daily vs weekly) and additional limitations (e.g., taking on an empty stomach and drug interactions) are important to understand in order to design a drug that appeals to the majority of patients and trumps competitor drugs. A study considering administration of T2DM medications showed that patients generally prefer a daily oral T2DM medication over a weekly injectable medication by a ratio of approximately 3:1 (when provided with no additional information and assuming both products are similar in terms of overall effectiveness, side effects and cost) [44]. In the AOM space, patient preference regarding the frequency of dosing may be a contributor to the success of the once weekly dosing regime of semaglutide compared with the once daily dosing of liraglitide [35]. However, the question of whether the oral or injectable route impacts patients is up for debate. It will be interesting to see how patients and the market reacts if Rybelsus, the once-daily oral version of semaglutide, which is currently in clinical trials, gains approval for the treatment of obesity. While Rybelsus is an oral form which could appeal to patients more, there is a requirement for it to be taken on an empty stomach and at a daily frequency, which as noted in the T2DM medication study, could have a negative impact on daily life that ultimately makes it undesirable. This is therefore another key aspect that pharmaceutical companies will need to think about when developing new drugs for the AOM market.

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Patient access: perhaps the biggest consideration for success

It is clear that improving solely weight loss efficacy is not the only way for a drug to become considered best-in-class in the AOM market, with weight maintenance, impact on ORCs and mode of administration all having the potential to play a key role in the success of new AOMs. On top of this, there are hurdles that need to be overcome in terms of access and reimbursement of AOMs, and there are also strategic positioning considerations to facilitate a new drug becoming the first choice for patients and physicians.

Unlocking reimbursement

Perhaps the greatest challenge for AOM contenders is to unlock access and reimbursement. This could be considered an area where the AOM market is most unique, in that obesity is perceived by countries such as Germany as a lifestyle choice rather than a clinical disease [5] and therefore AOMs are not publicly reimbursed. In the UK and USA, while obesity is recognized as a medical condition, there are several restrictions that limit reimbursement. England's NICE clinical guidelines recommend semaglutide for use within a specialist weight management service, many of which currently have long waiting list times, and for a maximum of 2 years of treatment. Semaglutide is also limited to patients with at least one weight-related comorbidity, either with BMI >35 kg/m^2 or BMI between 30 and 34.9 kg/m^2 and meet certain criteria for weight management service referral. In USA, Medicare currently does not cover AOMs broadly due to a provision excluding agents used for weight loss or weight gain. Medicaid covers Wegovy in some capacity for chronic weight management in 14 states and a minority of employer insurance plans cover AOMs: perhaps only about 22% of US employers. Whoever can unlock public reimbursement/insurance coverage of AOMs globally potentially stands to benefit greatly. Tactics may include outcome-based agreements, pricing strategies tailored to address budget impact concerns of payers, and/or the demonstration of the long term, wider benefits of AOMs (e.g. on payer-relevant ORCs and/or the demonstration of the need for continued treatment rather to remove payer enforced stopping rules). Indeed the SELECT data for semaglutide seems to have opened up wider reimbursement through Medicare and Medicaid in USA [45].

The out-of-pocket market versus public reimbursement/insurance

Alternatively, not all obesity treatments are currently paid via insurance or through public reimbursement. In many countries there is a large out-of-pocket market. Here, there is a greater role for effective marketing strategies, the success of which is noted above for Lipitor. Again, as patients themselves are paying, pricing needs to be considered in relation to competitors – will undercutting on price lead to success? Ultimately for patient access there are some strategic considerations to be made – will the focus be on public reimbursement/insurance or on patients paying themselves? Focusing on each segment has its advantages and disadvantages: with patients paying themselves, pricing could potentially be higher for this smaller market, but patients are less likely to adhere to treatment and solely focusing on this route of access will lead to inequity, further exacerbating the inequalities already existing in this therapeutic area. With public reimbursement/insurance coverage, pricing to unlock broad access will be an issue, but once achieved it is likely that more patients will adhere longer to treatment. The optimal solution to the price × volume × length of the treatment equation will need to be found. In terms of ORCs, it is plausible that some may be relevant to an out-of-pocket market even if not deemed payer relevant; further with patients paying themselves, convenience for this population is likely to be a significant value driver.

Positioning

With many different treatment options soon to be available (including many from the same manufacturer), being strategic in positioning of these medicines can help payers, prescribers and patients know when to best use them. For example, depending on their weight loss efficacy, medicines could be positioned based on starting BMI, with those with lower BMI needing a less efficacious product. More efficacious medicines could be used for those with a high BMI, or those already having or at a high risk of specific ORCs and/or those who have been unable to achieve a target weight loss on a less efficacious product (e.g., an escalation strategy).

Eli Lilly has taken a new step to position their obesity drugs at the forefront, launching LillyDirect which connects patients with independent providers who can prescribe AOMs such as Lilly's new drug Zepbound. This marketing approach offers a novel route for individuals to access AOMs, which will ultimately facilitate higher sales of AOMs like Zepbound. By having clear positioning, manufacturers can differentiate their product and potentially achieve a pricing premium.

Conclusion

It remains to be seen as to whether first-in-class, best-in-class or an entirely different strategy will underpin success in the AOM market. Given the highly competitive arena, alongside the substantial unmet need and associated healthcare and economic burden, pharmaceutical companies taking part in the AOM competition will need to spend time considering their strategy. Will they seek to differentiate on efficacy and/or price? If efficacy, will it be on weight loss or on ORCs? If ORCs, what should they demonstrate improvements in and what is the best trial design to prove benefits to stakeholders, but also have results read out before competitors? Importantly, whoever unlocks reimbursement opportunities and shapes the global perception of obesity from a lifestyle choice to a treatable disease will have a significant advantage. All of these factors will trade off against each other to determine the winner – apixaban (Eliquis; Bristol Myers Squibb/Pfizer), despite being the third to market, less convenient than the initial leading competitor (taken twice a day as compared with once a day for rivaroxaban (Xarelto; Janssen)), became the market leader in direct oral anti-coagulants because of its best-in-class clinical efficacy and a strong commercial strategy of demonstrating this profile through real-world data [46]. While it appears that Novo Nordisk and Eli Lilly are currently the front runners in the AOM race, there are numerous other drug candidates in the pipeline across the pharmaceutical industry: it seems that the race is just beginning, and only time will tell who will win it and how.

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Competing interests disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Writing disclosure

No writing assistance was utilized in the production of this manuscript.

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