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REVIEW ARTICLE

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Considerations for the design and conduct of pediatric obesity pharmacotherapy clinical trials: Proceedings of expert roundtable meetings

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Summary

Anti-obesity medications (AOMs) have emerged as one element of comprehensive obesity clinical care intended to improve long-term health outcomes for children and adolescents. The number of pediatric AOM clinical trials has burgeoned in recent years as new pharmacotherapeutics have been developed. Factors related to growth and development in children and adolescents can present unique challenges in terms of designing and conducting clinical trials investigating the safety and efficacy of AOMs. These barriers can delay the AOM development and evaluation process, increase the cost of performing trials, create challenges in the interpretation of results, influence the generalizability of the findings and present ethical dilemmas. In an effort to address these issues and provide guidance to streamline the process of designing and conducting pediatric AOM clinical trials, relevant key stakeholders convened a series of roundtable meetings to discuss, debate and achieve harmonization on design features. Stakeholder participants included a multidisciplinary group of international pediatric obesity experts, patient (parent) representatives and representatives from academic medicine, key regulatory agencies and industry. Topics of discussion included primary efficacy end-points, secondary end-points, eligibility criteria, trial run-in and follow-up phases, use of active comparators and guidelines for down-titration and/or stopping rules for excessive weight reduction. Consensus recommendations were agreed upon. Regarding end-points, emphasis was placed on moving away from BMI *z*-score as a primary outcome, incorporating multiple alternative BMI-related outcomes and measuring adiposity/body fat as a prominent secondary end-point. Trial eligibility criteria were carefully considered to maximize generalizability while maintaining safety. The limited value of trial run-in phases was discussed. It was also underscored that designing trials with extended follow-up periods after AOM withdrawal should be avoided owing to ethical issues (including possible psychological harm) related to weight regain without providing the opportunity to access other treatments. The panel emphasized the value of the randomized, placebo-controlled trial but recommended the thoughtful consideration of the use of active comparators in addition to, or instead of, placebo to achieve clinical equipoise when appropriate. Finally, the panel recommended that clinical trial protocols should include clear guidance regarding AOM down-titration to avoid excessive weight reduction when applicable.

KEYWORDS
anti-obesity medication, clinical trials, obesity, pediatric, pharmacotherapy

1 | INTRODUCTION

Clinical practice guidelines recommend the use of anti-obesity pharmacotherapy as part of a comprehensive treatment approach for children and adolescents living with obesity.[1,2] A growing number of pediatric anti-obesity medication (AOM) clinical trials have been performed in recent years, reflecting a steadily increasing development pipeline.[3–5] Unique factors related to growth and development in children and adolescents should be thoughtfully considered when designing and conducting obesity pharmacotherapy clinical trials, which in

many ways differ from studies conducted for adults, especially in consideration of body composition.[6] Lack of consensus regarding how pediatric AOM clinical trials should be designed and performed can delay the careful evaluation process of AOMs, increase the cost of performing trials, create challenges in the interpretation of results, influence the generalizability of the findings and present ethical dilemmas.

To address the challenges and inconsistencies in the design and conduct of pediatric AOM clinical trials, and to offer guidance for researchers, regulatory agencies and industry representatives, a series of two roundtable meetings (held in conjunction with ObesityWeek® 2022 and the European Congress on Obesity 2023) were convened to discuss, debate and achieve harmonization on design features. Roundtable participants included a multidisciplinary and international panel of pediatric obesity experts, patient (parent) representatives, as well as representatives from key regulatory agencies (United States Food and Drug Administration [FDA] and European Medicines Agency [EMA]), the United States Centers for Disease Control and Prevention, industry and the sponsoring organizations: The Obesity Society (TOS), European Association for the Study of Obesity (EASO), European Childhood Obesity Group (ECOG), Obesity Action Coalition (OAC) and European Coalition for People Living with Obesity (ECPO). Topics discussed included primary efficacy end-points, secondary end-points, eligibility criteria, trial run-in and follow-up phases, use of active comparators and guidelines for dose modification to avoid excessive weight reduction. Agendas were provided to participants prior to the roundtable meetings, which included the topics for discussion and pre-reading material consisting of relevant scientific literature pertaining to each topic. Each topic was presented by a roundtable member who briefly provided a summary of the literature and facilitated the group discussion. Consensus on topics was reached through an informal process of discussion at the roundtable meetings and subsequent email communication during the writing and review of the manuscript.

2 | CONSIDERATIONS FOR CLINICAL TRIAL DESIGN AND CONDUCT

2.1 | Primary efficacy end-point

One of the most important decisions to be made when designing a clinical trial is selecting an appropriate primary efficacy end-point. Roundtable experts agreed that the ideal primary end-point should reflect disease severity and pathology, track with important health outcomes such as cardiometabolic risk factors and quality of life, be relatively simple and cost-effective to perform, be reproducible, non-burdensome for participants and easy for researchers, clinical providers and patients/families to understand. The pediatric obesity intervention literature varies widely in terms of different body mass index (BMI) metrics that have been used as a primary end-point. This inconsistency has made it difficult to interpret results and compare the relative effectiveness of interventions and treatments across studies, including different AOMs.

One of the most commonly used BMI metrics is the *z*-score or standard deviation score. However, BMI *z*-scores derived from standard growth charts can be problematic when used in studies including children with severe obesity, an issue that may be more or less pronounced depending upon the growth chart used (e.g., World Health Organization [WHO] growth charts appear to be less susceptible to this issue), owing to sparse data at the extremes of the BMI distribution.[7–11] Therefore, roundtable experts strongly recommended against using change in BMI *z*-score as the primary efficacy end-point in pediatric obesity pharmacotherapy clinical trials. There was consensus that BMI-related metrics are not ideal primary end-points because they do not accurately reflect adiposity in all individuals. This is particularly true in the developing adolescent.[12] A standardized and robust metric capable of quantifying body fat mass and/or distribution would be an ideal primary or co-primary efficacy end-point with the caveat that additional research would need to validate these variables with clinical outcomes, at least in the context of being useful for regulatory approval. However, practical limitations must be considered especially when conducting multi-site and global clinical trials. Challenges of using dual energy x-ray absorptiometry (DXA) or magnetic resonance imaging (or other imaging modalities) include high cost, limited availability, radiation exposure (DXA), calibration and rigour/reproducibility of scanning procedures. Bioelectrical impedance was discussed as a potential option, but concerns were expressed regarding standardization and variability within measurements. Roundtable experts agreed that it is currently difficult to identify one metric that satisfies all of the criteria of an ideal primary efficacy end-point and that developing new techniques and technologies to quantify body fat represents a top-tier research priority. In the interim, roundtable experts recommended selecting non-*z*-score BMI metrics such as BMI (expressed as percent change), BMI percent of the 95th percentile (or BMI percent of other cut-off points for obesity, depending upon which growth references are used) or percent of the median BMI as the primary efficacy end-point for pediatric obesity pharmacotherapy clinical trials. Particularly for trials including younger children, age- and sex-adjusted metrics are ideal. Regardless of the specific BMI metric chosen as the primary end-point, it is recommended that multiple additional BMI-related metrics be reported as supportive secondary end-points so that comparisons can be made across studies.[11]

2.1.1 | Key points

- The ideal primary end-point should reflect disease severity and pathology, track with important health outcomes, be simple and cost-effective to perform, be reproducible and easy to understand.
- BMI *z*-score should not be used as a primary efficacy end-point in pediatric obesity pharmacotherapy clinical trials.
- Measures of body fat are preferred but practical considerations limit their use and additional research is needed to validate in relation to improvement of clinical outcomes.

- Multiple BMI-related metrics should be reported as secondary supportive end-points to allow comparisons across studies.

2.2 | Secondary end-points

Obesity is a complex, chronic, progressive, heterogenous and relapsing disease. For decades, BMI has been viewed as a phenotypic descriptor of adiposity despite its obvious flaws and imperfect estimates of body composition. In children and adolescents, considering body composition is of particular importance due to the complex interplay of growth and development, especially during puberty when sex hormones exert different impacts on both the fat and lean body mass.[13,14] Consequently, BMI can result in increased heterogeneity in terms of its estimation of adiposity. Considering the WHO definition of obesity, which focuses on fat mass and its interactions with risk of impaired health, it is apparent that more accurate phenotypic descriptors of obesity mirroring the heterogenous spectrum of disease are needed (both in context of body composition and health risk). Therefore, in relation to key secondary end-points in pediatric obesity pharmacotherapy clinical trials, roundtable experts proposed shifting the attention and priorities to obtain precise measures of the amount of body fat and its distribution, which can be accomplished with DXA scans, magnetic resonance imaging or bioelectric impedance measurements when available. If these methods are unavailable, measures of waist and hip circumference could be included since increased visceral adiposity has been associated with several cardiometabolic outcomes.[15,16] It was suggested that the field move towards establishing easy-to-use reference curves and percentiles for each body composition assessment modality that covers the entire pediatric population and is specific for age, sex and ethnicity.[17–19] Innovative approaches to the assessment of body fat incorporated into clinical trials would shed light on the degree to which adiposity reduction can improve other important secondary outcomes such as cardiometabolic health, physical function including movement and gross motor skills and psychosocial health including quality of life, which may be affected by the degree of excess body fat. Roundtable experts also discussed the need to define metrics of adiposity reduction that could be considered 'treating to target'. That is, establishing goals for achieving an optimal or ideal degree of body fat reduction while preserving lean body (muscle and bone) mass.

Finally, roundtable experts recognized the critical importance of moving beyond the traditionally weight/BMI-centric focus and assessing other health outcomes such as cardiometabolic risk factors (e.g., blood pressure, lipid profile, glycemic outcomes, inflammation, etc.), quality of life, mental health and physical function/mobility in the context of pediatric obesity pharmacotherapy clinical trials. Increasing emphasis can be placed on incorporating patient reported outcomes in future intervention research, including identifying minimally important differences in these domains from the perspective of youth living with obesity and their caregivers. In so doing, it will be critical to solicit input from children/adolescents living with obesity and their caregivers in order to properly inform the design of these studies.

2.2.1 | Key points

- Key secondary end-points should include measures of body fat/adiposity.
- Ideally, easy to use reference curves and percentiles for body composition measures would be developed.
- There is a need to define metrics of ideal adiposity reduction (i.e., 'treating to target')
- Additional health outcomes, such as cardiometabolic risk factors, quality of life, mental health and physical function should be incorporated into clinical trials.

2.3 | Eligibility criteria and generalizability

According to guidance provided by the FDA, 'effort should be made to include in the studies a representative sample of patients from the various demographic, ethnic, and racial groups in which the prevalence of obesity is highest (https://www.fda.gov/media/71252/download)'. Therefore, taking an overly restrictive approach to excluding participants would potentially be in conflict with the concept of generalizability. Roundtable experts agreed that a higher priority should be placed on recruiting/enrolling more diverse cohorts that include historically marginalized groups and that intervention and study design features should consider the unique factors that make it difficult for individuals to participate in clinical trials (e.g., high number of study visits and requirements to attend many/most visits in-person). Preplanned subgroup analyses can help explain the heterogeneity of treatment effects, including factors such as sex and socio-economic status. The EMA Committee for Medicinal Products for Human Use states in a guideline on clinical evaluation of medicinal products that eligible patients are those 'for whom at least one trial of an appropriate weight-reducing diet has proven to be insufficient'.[20] The FDA also recommends that the lifestyle modification programmes used in the pre-approval trials should be applicable to the types of patients prescribed the product in the post-approval setting (https://www.fda.gov/media/71252/download). In this context, generalizability may be limited in that many patients may not have access to comparable lifestyle modification programmes delivered in clinical trials.

The potential negative consequence of overly restrictive exclusion criteria is that once approved, these AOMs may be clinically prescribed to youth not necessarily represented in the trials. This particularly applies to individuals with both obesity and mental health challenges since the complex bidirectional relationships between mental health and obesity serve to potentiate the severity and interdependency of each.[21] Some AOMs may have the potential for clinically significant neuropsychiatric adverse events. Therefore, although the EMA recommends that individuals with a history of mild to moderate depression and those using anti-depressive treatment should not be excluded from AOM clinical trials,[20] youth with more severe mental health issues have so far been excluded from many studies,[3–5] which limits generalizability. This exclusion could be because some adult

clinical trials for certain AOMs have excluded individuals with specific mental health comorbidities.

Roundtable experts highlighted the need to be more 'inclusive' by loosening the exclusionary criteria to be more representative of the end-user population. Specifically, a recommendation was made to consider inclusion of individuals historically excluded from trials because of, for example, major depressive disorder within 2 years before screening, diagnoses of severe psychiatric disorders or bulimia nervosa and/or a history of suicide attempt, with the provision that the individuals are stable at the time of enrollment and resources are made available to ensure safety monitoring and support during the study. Roundtable experts also agreed that individuals currently using medications known to affect weight (e.g., metformin, stimulants, certain anti-psychotics), but not considered AOMs, should not necessarily be excluded from trial eligibility if the dose of such medications are stable prior to enrollment. Recommendations also included that the standard exclusion criterion: 'Any disorder…which in the investigator's opinion might jeopardize the subject's safety….' needs to be more specific to enhance standardization and generalizability. Finally, roundtable experts agreed that monogenic or syndromic obesity may not necessarily be exclusionary for all trials, acknowledging the challenges and additional potential safety concerns, and the fact that limited sample sizes of these patient populations may be insufficient to justify a label change/expansion.

2.3.1 | Key points

- Efforts should be made to reasonably limit exclusionary criteria to improve generalizability.
- Increasing the number of participants with stable mental health conditions would improve representativeness but will likely require additional safety monitoring and support.
- Monogenic or syndromic obesity should not necessarily be exclusionary for all trials if appropriate safety precautions are implemented.

2.4 | Run-in and follow-up phases

A run-in phase consisting of lifestyle therapy before randomization to a pharmacological intervention is a common design element of regulatory clinical trials examining the safety and efficacy of AOMs in children and adolescents.[22] Such run-in phases allow for pre-randomization assessment of study visit and procedure compliance and response to lifestyle therapy, as well as subsequent exclusion of participants based on pre-specified criteria. Although there is little to no evidence to support it, excluding participants who demonstrate suboptimal adherence with study visit and/or procedure aspects during a lifestyle therapy run-in phase could potentially reduce attrition in the main part of the trial, which, in turn, may be cost-saving and may improve the validity of results. Excluding participants who respond to a lifestyle therapy run-in phase by reducing BMI below the obesity threshold may avoid unnecessary exposure to AOMs in participants who do not need pharmacological intervention to reduce weight. However, this has proven to be a small fraction of the sample for recent trials that have utilized this design feature.[3,5]

The advantages of a lifestyle therapy run-in phase must be weighed against the disadvantages. By excluding participants with suboptimal compliance, the generalizability of the trial results may be limited. Exclusion of participants who respond to lifestyle therapy may also over- or under-estimate the treatment effect of the AOM, although this has been a variable finding. One study examining the association of run-in phases with weight reduction in adult obesity treatment trials found no difference in 72 pharmaceutical trials of which 29% used a run-in phase.[22] Another potential disadvantage is that an excessively long run-in phase can be costly and may hinder recruitment if potential participants have already tried to lose weight on their own. Engaging in a lifestyle therapy run-in phase for these participants may be viewed as overly burdensome. Finally, there is regulatory discordance on this issue. The EMA recommends 3 to 6 months of lifestyle therapy run-in for AOM clinical trials[20] while the FDA guidance is to only require documentation of a history of failing to lose sufficient weight with lifestyle therapy (https://www.fda.gov/media/71252/download).

The roundtable experts discussed the pros and cons of a short (e.g., no more than 1 month) lifestyle therapy run-in phase that may serve to build relationships between the participants and research team, which in turn may reduce attrition and allow for more time to assess participants whose mental health status may be undefined. However, the majority of roundtable experts agreed that a lifestyle therapy run-in phase is unnecessary in the context of pediatric AOM trials, and that documentation of a failed prior weight loss attempt with lifestyle therapy is sufficient to identify participants that may benefit from pharmacological interventions. Relatedly, roundtable experts also recommended documentation of weight stability prior to enrollment given that pretreatment weight reduction has been associated with better outcomes in behavioural trials in adults, thus potentially confounding the interpretation of the results.

Follow-up phases of clinical trials serve to quantify longer-term outcomes after the intervention under investigation has been withdrawn, including possible harms from the intervention. For AOM clinical trials, the ostensible purpose may be to identify the change in BMI or weight trajectory after withdrawal of the treatment and any residual harms of AOMs (e.g., incidence of disordered eating behaviours, mental health problems, etc.). However, it is currently well established that discontinuation of AOM in a person with obesity usually results in weight regain,[3,23] as recurrence in the absence of treatment is a hallmark feature of a chronic disease. Continuing to employ a follow-up phase to document this effect in future pediatric obesity, pharmacotherapy trials were deemed unethical by roundtable experts because it potentially limits participant access to effective treatments and sets the stage for inducing physical and mental harm associated with weight regain. Additionally, follow-up phases can be costly and do not address the uncertainty of long-term (i.e., beyond 6 months) effects of the intervention. Therefore, roundtable experts strongly

recommended against the use of follow-up phases without treatment access in most clinical trials. However, clinical registry studies and/or pragmatic trials could serve a useful role in characterizing potential residual risks following medication withdrawal.

In contrast, open-label extension phases can generate additional data regarding effectiveness, safety (including potential identification of rare adverse events) and tolerability in the context of longer-term exposure to active treatment. Indeed, determining the long-term effects of AOMs in children and adolescents is of critical importance. Simultaneously, an open-label extension may be an opportunity to provide compassionate care to participants who may not otherwise have access to AOMs. Multiple ethical considerations related to open-label extension phases require further discussion and clarification before they are widely employed. For example, should participants be given access to active treatment after trial participation without knowing their group assignment during the trial? Who is responsible for providing active treatment? What is an appropriate duration of the open-label extension? Finally, participants must be informed about the potential changes in the AOM landscape that may occur during the open-label phase. The recent pace of regulatory approval of AOMs for youth has been brisk, and more effective treatments than that being studied may be available to participants before the end of the open-label extension phase.

2.4.1 | Key points

- Lifestyle therapy run-in phases may have limited value in the context of pediatric obesity AOM trials; documentation of a failed prior weight loss attempt with lifestyle therapy is sufficient to identify participants who may benefit from pharmacotherapy.
- Utilizing extended follow-up phases after AOM is withdrawn was deemed unethical because it limits participant access to potentially effective treatments.
- Open-label extension phases may allow for collecting effectiveness and tolerability data in the context of longer-term exposure to active treatment.

2.5 | Active comparators and placebo

The gold standard for testing efficacy and safety of AOMs for the treatment of pediatric obesity is the randomized, placebo-controlled clinical trial. However, the use of a placebo for these trials poses potential ethical challenges. Although not unique to AOM studies, many children and adolescents may not have the maturity or knowledge to make informed decisions about their health, underscoring the importance of proper assenting and consenting procedures in clinical trials.[24] This is compounded by the fact that obesity in children is a progressive disease and the use of a placebo may lead to substantial and potentially lasting increases in obesity severity. This is true even though studies, to date, employ a background of lifestyle therapy for both the treatment and placebo arms. Lifestyle therapy alone may not limit the progression of obesity for some individuals, especially in those who are most seriously affected.[25]

The Declaration of Helsinki and U.S. Code of Federal Regulations both provide guidance on the use of placebo. When testing the efficacy and safety of a new intervention, the Declaration of Helsinki supports the use of a placebo as a comparator, instead of the best proven intervention, only in the following circumstances: when there is no proven intervention, when there is 'compelling and scientifically sound methodological reasons' to not use the best proven intervention, and when participants who receive placebo will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). Based on these criteria, the ethics of using a placebo in pediatric AOM trials is unclear. The United States Code of Federal Regulations, Title 45, Part 46, Subpart D, in regard to safeguards for children (a vulnerable population) involved in research, indicates that in studies with the prospect of direct benefit, such as AOM clinical trials, the risk posed by the intervention may be justified if the anticipated benefits are at least as favourable as presented by available alternatives (https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/common-rule-subpart-d/index.html). Yet, what is considered an available alternative in terms of pediatric obesity treatment is quite variable especially in the context of global trials. Some participants may have access to recently FDA- or EMA-approved AOMs through their clinical affiliations, while others may not even have access to lifestyle therapy.

An alternative to a placebo-controlled trials are active comparator trials, which compares the intervention under investigation to current proven interventions.[26] Importantly, however, these trials test inferiority. That is, non-inferiority trials aim to show that an experimental treatment is not less effective than an active control by more than the equivalence margin. Such trials require large sample sizes and may make interpretation of results and adverse events more challenging.[27] Active comparator trials for AOMs may be possible in the future when more data are accumulated on the safety and efficacy of various medications.

The roundtable panel recognized that placebo-controlled trials for examining new AOMs for pediatric obesity are necessary and justified at the present time.[28] In relation to characterization of adverse events, placebo groups provide the necessary control to properly identify the true incidence of emergent side effects. Notably, participants receiving placebo do, in fact, receive treatment in the form of lifestyle therapy. In other words, treatment is not completely withheld, and some participants, albeit commonly a relatively small percentage, respond to lifestyle therapy alone. Further, the lifestyle therapy offered in many trials is often more robust than what can be found in clinical or community settings. Therefore, it is likely that participants receiving placebo may receive better care than would be available to them had they not participated in the trial.

Provisional to recommending the use of placebo-controlled studies, the panel supported scrupulous precautions in order to minimize risk.[29] These might include reasonable limitations on the duration of

use of placebo versus active medication within trials to the minimum time required for scientific validity and regulatory approval in order to limit exposure to placebo; 1 year of exposure to the maximum dose (or maximal tolerated dose) of active treatment or placebo was suggested as a potential option. The panel also recommended consideration of including protocol stipulations for using 'rescue' medications or study withdrawal for situations where the participants experience substantial BMI increase. Finally, the panel agreed that assent and consent forms should include explicit language stating that participants assigned to placebo may be at risk of progressive weight gain that may not be reversible without a different form of treatment.

2.5.1 | Key points

- Since pediatric obesity is a progressive disease, the use of placebo alone (with lifestyle therapy) may lead to weight gain in some participants.
- Active comparator trials can be challenging to conduct since they require large sample sizes owing to the focus on non-inferiority.
- Continued use of placebo-controlled designs is necessary to accurately estimate efficacy and safety of new medications; they are currently justified in the pediatric population if robust lifestyle therapy is offered; this may change in the evolving therapeutic landscape.
- Incorporating design features such as limiting the time of exposure to placebo, use of rescue medications or study withdrawal in the context of significant weight gain and explicit language in the assent and parental consent forms about potential risk of weight gain are encouraged.

2.6 | Excessive weight reduction

As our understanding of obesity and its physiology has evolved, so too has the development of effective AOMs. Historically, medications targeting obesity had been fraught with certain safety concerns including cardiovascular risk or psychiatric events (e.g., sibutramine, fenfluramine and rimonabant).[30] In addition, many medications initially developed for obesity treatment demonstrated minimal change in body weight and could not meet the 1 year efficacy benchmarks of ≥5% weight loss from baseline with at least 35% of the study population losing ≥5% body weight from baseline, set by the FDA for approval (https://www.fda.gov/media/71252/download). With the development of the newest AOMs over the past 10 years, the degree of weight reduction is now beginning to approach that observed with metabolic and bariatric surgery procedures.[31] Moreover, multiple clinical trials in adults utilizing semaglutide or tirzepatide and adolescents using semaglutide have demonstrated significant heterogeneity in body weight changes, with some participants achieving substantial weight reduction and others experiencing weight gain.[5,32,33]

Roundtable experts recommended that protocols should not be overly prescriptive about weight/BMI-based decision rules other than in extreme cases where a participant moves, or has a high potential of moving, into the underweight category. However, protocols should provide general guidance to site principal investigators if concerns about excessive weight reduction arise. Examples of potential concerns may include inappropriate loss of lean mass, reduction in bone mineral density and/or inadequate micronutrient intake (all of which could be assessed in future clinical trials). In assessing excessive weight reduction, additional considerations (e.g., body fat; attitudes/feelings of participants/families; mental health; etc.) should also be discussed in the context of adjusting or stopping the study intervention.

Multiple suggestions around weight reduction thresholds, the effect of puberty on these thresholds and the rapidity of meeting these thresholds were discussed. Setting a low threshold at some point above the underweight cut point, from the 25th to 50th BMI percentile for age and sex, was considered. Ultimately, roundtable experts settled on weight reduction crossing the 50th BMI percentile as a point when the dose of study medication could be stabilized and not escalated further. Furthermore, avoiding withdrawal of study medication while considering dose maintenance or down-titration should be the goal when there are concerns about excessive weight reduction. Innovative designs involving re-randomization (e.g., to lower doses) could be considered while also including more frequent weight assessments (e.g., using remote scales or asking participants to self-weigh and report to study staff between in-person visits). Finally, enhancing education at baseline about the potential rapidity and degree of weight reduction, reviewing recommendations for maintaining nutritional quality as appetite decreases and satiety increases (i.e., getting the most out of the calories consumed—similar to post-metabolic and bariatric surgery nutritional counselling) and regular monitoring of nutrient intake should be emphasized in pediatric obesity pharmacotherapy clinical trials. Future studies could be designed to address whether providing specific nutritional recommendations in the context of AOM use could maximize the health benefits of therapy.

Consensus was reached that clinical trial protocols need to carefully address the rapidity and degree of weight reduction while trying to avoid strict decision rules other than potentially identifying a minimum lower threshold of BMI reduction that would trigger maintaining a dose or potentially de-escalating a dose, keeping participant safety at the forefront. Increased attention to counselling about having a well-balanced diet and more frequent monitoring of weight during a trial are also warranted when conducting pediatric obesity pharmacotherapy clinical trials.

2.6.1 | Key points

- Protocols should not be overly prescriptive about weight-based decision rules other than in cases where participants move to or are on a trajectory to move into the underweight category.
- Protocols should provide general guidance if concerns about excessive weight reduction arise.

- Weight reduction crossing the 50th BMI percentile may be a point when the dose of study medication should be stabilized and not escalated further.
- Enhancing education about the potential rapidity and degree of weight reduction, reviewing tips for maintaining nutritional quality and regular monitoring of nutrient intake should be emphasized.

3 | CONCLUSION

Unique factors relevant to the developing child and adolescent have presented challenges and opportunities in terms of best practices for designing and conducting pediatric AOM clinical trials. To offer guidance in these areas, relevant key stakeholders convened a series of roundtable meetings to discuss, debate and achieve harmonization on design features. Consensus recommendations were agreed upon including: discouraging the use of BMI z-score as a primary outcome; incorporating multiple alternative BMI-related outcomes; measuring body fat as a prominent secondary end-point; carefully designing trial eligibility criteria to maximize inclusion and generalizability; reducing the use of lifestyle therapy only run-in phases and eliminating extended medication withdrawal follow-up phases; incorporating thoughtful consideration of the use of active comparators in addition to, or instead of, placebo to achieve clinical equipoise when appropriate; and inclusion of clear guidance and dose modification rules in protocols to avoid excessive weight reduction when applicable.

CONFLICT OF INTEREST STATEMENT

Dr. Aaron S. Kelly engages in unpaid consulting activities for Boehringer Ingelheim, Eli Lilly, Novo Nordisk, and Vivus; engages in unpaid educational activities for Novo Nordisk; receives donated drug/placebo from Vivus and donated drug from Novo Nordisk for National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-funded clinical trials. Ms. Melanie Bahlke has received consulting honoraria from Novo Nordisk and Boehringer Ingelheim. Dr. Jennifer L. Baker has received consulting honoraria from Novo Nordisk A/S. Dr. Carine de Beaufort has no disclosures. Dr. Ruth M. Belin is an employee and shareholder of Eli Lilly and Company. Dr. Helena Fonseca has no disclosures. Dr. Paula M. Hale is an employee and stockholder of Novo Nordisk. Dr. Jens-Christian Holm conducts clinical trials for Novo Nordisk through contracts paid directly to his institution and has received consulting honoraria from Novo Nordisk A/S and Rhythm Pharmaceuticals. Dr. Jens-Christian Holm provides training, treatment, and digital tools. Dr. Daniel S. Hsia conducts clinical trials for Novo Nordisk, Vivus, and Eli Lilly through contracts paid directly to his institution. He does not receive any funds directly from these sponsors. Dr. Ania M. Jastreboff conducts multi-center trials with Eli Lilly, Novo Nordisk, and Rhythm Pharmaceuticals; serves on scientific advisory boards for Amgen, AstraZeneca, Boehringer Ingelheim, Biohaven, Eli Lilly, Intellihealth, Novo Nordisk, Pfizer, Rhythm Pharmaceuticals, Scholar Rock, Structure Therapeutics, Terms Pharmaceutical, WeightWatchers, Zealand Pharmaceuticals; and receives institutional grant funding from the NIDDK. Dr. Petur B. Juliusson has no disclosures. Dr. Madhumita Murphy is an employee and shareholder of Eli Lilly and Company. Dr. Jonathan Pak is an employee of Boehringer Ingelheim Pharmaceuticals, Inc. Ms. Elizabeth Paul has served on patient advisory committees for Pfizer and Boehringer Ingelheim; she has delivered presentations for Eli Lilly and Boehringer Ingelheim. Dr. Bryan Rudolph is an employee of Boehringer Ingelheim Pharmaceuticals. Dr. Gitanjali Srivastava has received lecture fees and honoraria from Novo Nordisk and Rhythm and conducts clinical trials for Eli Lilly. Dr. Christoffer W. Tornøe is an employee and stockholder of Novo Nordisk. Dr. Daniel Weghuber has received lecture and consulting honoraria from Novo Nordisk. Dr. Claudia K. Fox conducts clinical trials for Novo Nordisk and Eli Lilly through contracts paid directly to her institution. She does not receive any funds directly from these sponsors.

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