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The Missing Piece in Obesity Treatment May Be Long-Term Weight Maintenance

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At BIO 2026, Steffen-Sebastian Bolz, MD, Ph.D., Founder and Chief Scientific Officer of Aphaia Pharma, discusses why the future of obesity treatment will extend beyond incretin therapies, highlighting the potential of physiological nutrient sensing, long-term weight maintenance, and improved tolerability as the next frontier in metabolic disease management.

As obesity treatment enters a new phase of innovation, the industry is increasingly looking beyond GLP-1 therapies to address persistent challenges such as treatment adherence, long-term weight maintenance, and patient accessibility.**At BIO International Convention 2026 in San Diego, BioSpectrum Asia spoke with Steffen-Sebastian Bolz, MD, Ph.D., Founder and Chief Scientific Officer of Aphaia Pharma, about the company's novel approach**to restoring natural nutrient sensing mechanisms, the emerging role of circadian biology in metabolic health, and why future obesity care will require a broader therapeutic toolbox rather than a single dominant drug class

The obesity market is dominated by GLP 1 therapies. Why is now the right time for alternative approaches?

The obesity market has been transformed by GLP-1 therapies, but their success has also highlighted the need for additional treatment options. Obesity is a chronic, relapsing disease that often requires long-term management, yet current GLP-1-based therapies continue to face important challenges related to tolerability, adherence, accessibility, and cost. Gastrointestinal side effects remain a significant reason for treatment discontinuation, while supply constraints and reimbursement limitations mean that many eligible patients still lack access to effective therapies.

At the same time, the obesity market is rapidly evolving from a single-category opportunity into a highly segmented therapeutic landscape. Patients differ substantially in disease severity, comorbidities, treatment goals, preferences for route of administration, dosing frequency, and tolerance of side effects. As the market matures, differentiation will increasingly depend not only on the magnitude of weight loss, but also on long-term tolerability, preservation of muscle and bone mass, cardiometabolic outcomes, and the ability to maintain weight loss over time.

Importantly, one of the greatest unmet needs remains the prevention of weight regain following treatment cessation. This challenge underscores the need for therapies that address complementary biological pathways involved in energy balance

and metabolic regulation. Looking ahead, innovation will need to extend beyond the now-established incretin paradigm and target novel mechanisms that can be used alone or in combination with existing treatments.

In this future landscape, orally administered therapies with improved tolerability, suitability for long-term use, and the potential to support durable weight maintenance are likely to play an increasingly important role. Meeting these objectives will require innovation beyond the classical incretin system and the development of entirely new therapeutic approaches to obesity.

Could restoring natural nutrient sensing become a complementary strategy to GLP 1 medicines?

Absolutely. Restoring natural nutrient sensing has the potential to become an important complementary strategy to GLP-1-based therapies, particularly in the context of long-term weight management and treatment maintenance. While GLP-1 agonists have demonstrated impressive efficacy in inducing weight loss and reducing cardiovascular risk, real-world experience has shown that up to 60% of patients discontinue treatment within the first 12 months, often due to gastrointestinal side effects, tolerability concerns, treatment burden, or access limitations.

This is a critical challenge because the cardiovascular and metabolic benefits of weight loss can only be fully realized when patients remain on therapy long enough to sustain meaningful reductions in body weight and cardiometabolic risk factors. High discontinuation rates therefore limit the population-level impact of these otherwise highly effective medicines.

Aphaia's approach, which aims to restore physiological nutrient sensing mechanisms, could address this unmet need. Based on approximately 300 patients treated across two Phase 2 studies, our oral glucose formulation has demonstrated a virtually complete absence of treatment-related adverse effects, supporting its suitability for long-term use. If the competitive weight loss results anticipated following unblinding of our Phase 2 study in Q3 2026 are confirmed, the therapy could serve both as a maintenance strategy following GLP-1 treatment and as an alternative option for patients unable or unwilling to use incretin-based therapies.

Importantly, given the continued limitations in access to obesity treatments and the vast number of underserved patients, novel approaches should not be viewed solely as competitors to GLP-1 medicines. Rather, they represent a necessary expansion of the therapeutic toolbox to improve outcomes across a broader patient population.

What have you learned from your ongoing obesity studies that surprised you most?

The most surprising insight from our ongoing obesity studies has been the extent to which the body's nutrient-sensing system can be therapeutically harnessed when stimulated in a physiologically appropriate manner. Aphaia's treatment strategy is fundamentally novel: rather than directly activating hormonal pathways pharmacologically, we recruit the body's own nutrient-sensing cells to restore physiological signaling processes that are disrupted in obesity. This is a technically demanding approach that, to our knowledge, has never been clinically validated before.

Our studies have not only confirmed the core concept - that targeted stimulation of nutrient-sensing cells in the distal small intestine triggers a coordinated endocrine, neuroendocrine, and neural response - but have also revealed the critical importance of timing. We have learned that the effectiveness of these responses is closely linked to the body's circadian rhythm, creating an opportunity not only to activate physiological pathways but also to retrain disrupted metabolic rhythms that frequently accompany obesity.

Perhaps even more exciting is the emerging realization that restoring and maintaining these natural rhythms may influence food intake patterns beyond the treatment period itself. This raises the possibility that weight loss achieved through physiological nutrient sensing could prove more durable and sustainable after treatment cessation. If confirmed, this would represent an important advance in obesity management, addressing one of the field's greatest challenges: maintaining long-term weight loss rather than simply inducing it.

How do you see the obesity treatment landscape evolving over the next five years?

Over the next five years, the obesity treatment landscape will become more diverse, more competitive, and more personalized. As previously discussed, GLP-1 and incretin-based therapies have transformed the field, but they will not be the final answer for all patients. Obesity is a chronic, heterogeneous disease, and the market will increasingly segment by

patient profile, comorbidities, route of administration, tolerability, dosing burden, long-term adherence, and the ability to preserve weight loss after treatment cessation.

As more therapies enter the market, differentiation will shift beyond the magnitude of weight loss alone. Durability, cardiovascular and metabolic outcomes, preservation of muscle and bone mass, safety, convenience, and suitability for long-term use will become increasingly important. Real-world evidence will also play a central role in determining reimbursement decisions and broader public health adoption.

This creates significant opportunities for approaches beyond the traditional incretin system. Oral therapies, better tolerated drugs, maintenance treatments following GLP-1-induced weight loss, and mechanisms that restore physiological regulation of appetite and metabolism are likely to become increasingly relevant. Ultimately, the future of obesity care will not be defined by a single dominant drug class, but by a broader therapeutic toolbox that allows physicians to tailor treatment strategies to individual patient needs and different stages of disease.

What unmet need remains largely ignored in metabolic disease today?

Before answering, it may be worth replacing the term “ignored” with “underaddressed.” Most of these areas are recognized by researchers and industry participants, but they receive far less attention and investment than the current focus on incretin-based weight-loss therapies.

Among the most underaddressed needs is the prevention of weight regain following treatment cessation. While enormous resources are being devoted to inducing weight loss, comparatively little attention is paid to sustaining it over the long term. Yet durable weight maintenance is arguably the defining challenge in obesity management and will ultimately determine the long-term clinical and economic value of any therapy.

A second underaddressed area is the restoration of physiological nutrient sensing. Current therapies predominantly act downstream by modulating hormonal signaling pathways, such as GLP-1 and GIP. Far less effort is directed toward correcting the upstream biological mechanisms that govern nutrient sensing, appetite regulation, and energy homeostasis. Restoring these natural control systems may offer a more physiological and potentially sustainable approach to metabolic disease management.

Circadian and meal-timing biology represent another significant opportunity. Growing evidence suggests that obesity is not only a disorder of energy balance but also one of disrupted metabolic rhythms. However, relatively few therapeutic programs are specifically designed to restore or retrain these rhythms despite their profound influence on food intake, metabolism, and body weight regulation.

Finally, long-term tolerability and treatment adherence remain underappreciated challenges. The ultimate goal of obesity therapy should not be weight loss itself, but the reduction of cardiovascular and metabolic risk. Patients can only realize these benefits if they remain on treatment long enough to achieve and sustain meaningful health improvements, making tolerability and adherence critical determinants of real-world success.

What is the single biggest takeaway from BIO 2026 that will influence your company's strategy over the next 12 months?

The single biggest takeaway from BIO International 2026 was the realization of how strongly Aphaia’s treatment paradigm aligns with the direction in which the obesity field is evolving.

Dedicated sessions at BIO have examined obesity not simply as a weight management challenge but as a complex metabolic disease requiring more nuanced, durable solutions. Throughout our discussions with investors, pharmaceutical companies, clinicians, and other stakeholders, it is becoming increasingly clear that the conversation is shifting beyond weight loss alone. Greater attention is now being paid to several historically underaddressed needs, including long-term weight maintenance, improved tolerability and adherence, restoration of physiological metabolic regulation, and the role of circadian and nutrient-sensing pathways in obesity.

These are precisely the areas where Aphaia’s approach is differentiated. By targeting the body’s natural nutrient-sensing mechanisms, we aim not only to support weight loss but also to address some of the underlying physiological drivers of metabolic dysfunction. Equally important, our clinical experience to date suggests the potential for excellent tolerability, a

prerequisite for chronic treatment and the sustained realization of cardiovascular and metabolic benefits.

With efficacy data expected soon, we believe we are approaching the final piece of the puzzle. BIO 2026 reinforced our conviction that Aphaia is developing a solution that addresses several important gaps in the current treatment landscape. As a result, we look forward to the next phase of partnering discussions with increased confidence, knowing that our approach has the potential to complement existing therapies while filling critical unmet needs that are becoming increasingly recognized across the obesity community.