American Diabetes Association.

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News Release

Contact: Rebecca Fisher, 703-253-4918
SciSessionsPress@diabetes.org

Late Breaking Weight Loss Innovations: New Drug Therapies Shown to Offer Positive Outcomes for Obesity and Type 2 Diabetes Management

Novel Weight Loss Drug, Survodutide, Shows Significant Weight Loss of Nearly 19% At 46 Weeks

Oral Semaglutide Demonstrates Weight Loss Up to 15% for People with Obesity and Improved Management of Type 2 Diabetes

SAN DIEGO, CA, JUNE 25, 2023 – Late breaking data focused on new drug therapy innovations to treat obesity were presented at the American Diabetes Association's® (ADA) 83rd Scientific Sessions in San Diego, CA. Two of the studies were also simultaneously published in *The Lancet*.

This comes at a time when more than 37 million Americans live with diabetes, and nearly 90% of people with diabetes are overweight or have obesity. More than 100 million Americans currently live with obesity, and the number is steadily climbing. By 2030, half of all Americans will have obesity. Despite this, existing treatment options have demonstrated limited effectiveness.

"Addressing the twin epidemics of obesity and diabetes is critical to slowing the trajectory of this ongoing public health crisis. We have seen an explosion of promising new research and innovations in this field in recent years," said Dr. Robert Gabbay, chief scientific and medical officer for the ADA. "The studies presented at this year's annual meeting are game-changers in the way we customize treatment for individuals with obesity and those with type 2 diabetes."

Novel Drug Treatment for Obesity Shown Effective Up to 46 Weeks

Results from a phase 2 clinical trial of survodutide (also known as BI 456906), a novel dual glucagon receptor (GCGR) and glucagon-like peptide 1 receptor (GLP-1R) agonist, showed up to 18.7% weight loss in overweight or obese individuals through a 46-week time frame.

The randomized, double-blind, placebo-controlled, dose-finding trial, enrolled 387 participants with a body mass index (BMI) of 27 kg/m2 or higher, who were randomly assigned to receive weekly subcutaneous injections of survodutide at varying doses (0.6 mg, 2.4 mg, 3.6 mg, or 4.8 mg) or a placebo for a duration of 46 weeks. The study included a 20-week rapid, bi-weekly dose escalation phase, followed by a 26-week maintenance phase. The primary endpoint was the percentage change in body weight from baseline at week 46, and secondary endpoints included

the proportion of participants achieving at least 5%, 10%, or 15% weight loss from baseline at week 46.

The results of the study demonstrated a clear dose-response relationship, with increasing doses of survodutide correlating with greater reductions in body weight. At week 46, participants in the survodutide group achieved substantial weight loss compared to the placebo group. The mean body weight reductions were as follows: 0.6 mg (-6.2%), 2.4 mg (-12.5%), 3.6 mg (-13.2%), and 4.8 mg (-14.9%), compared to -2.8% in the placebo group. At 46 weeks, patients reaching and staying on 4.8 mg survodutide achieved a weight loss of 18.7%. Notably, 82.8% of participants in the 4.8 mg BI 456906 group achieved a weight loss of at least 5% at week 46, compared to only 25.9% in the placebo group.

The study also evaluated the safety profile of survodutide. Adverse events were reported in 90.9% of participants in the survodutide group, with the majority being gastrointestinal in nature. In placebo group, adverse events were reported in 75.3% of participants. However, no unexpected safety concerns were identified over the 46-week study period. Serious adverse event incidence was comparable between the survodutide group (4.2%) and the placebo group (6.5%).

“We are encouraged by the significant weight loss observed in the phase 2 study results which will pave the way for further research,” said Carel le Roux, MBChB, Ph.D., Professor at University College in Dublin, Ireland, and Principal Investigator. “By activating both the glucagon and GLP-1 receptors, survodutide may inhibit both appetite and improve energy expenditure. The findings not only show significant weight loss with increasing doses of survodutide, but we also saw a favorable safety profile, reinforcing the potential clinical benefits.”

The authors of this study anticipate upcoming Phase III trials and are committed to continuing to explore the potential of survodutide to provide a much-needed treatment option for the billions of people with obesity.

Once-Daily Oral Semaglutide Shown Effective For Weight Loss

Oral semaglutide is available at 14 mg for the treatment of type 2 diabetes (T2D); however, the OASIS 1 study is the first time it has been investigated for both the treatment of obesity and at the higher 50 mg dose. The research found that once-daily oral semaglutide 50 mg resulted in superior and clinically meaningful weight loss of 15.1% compared with placebo when used alongside diet and physical activity in adults with overweight or obesity without T2D. Findings were simultaneously published in *The Lancet*.

The double-blind, randomized, controlled phase 3 trial enrolled a total of 667 participants from 50 outpatient clinics across Asia, Europe, and North America. Participants had a body mass index (BMI) of at least 30 kg/m² or at least 27 kg/m² with weight-related complications and/or

comorbidities but did not have T2D. The trial also incorporated a lifestyle intervention alongside the treatment.

Participants were randomly assigned to receive either oral semaglutide escalated to 50 mg or visually matching placebo once a day for 68 weeks. The coprimary endpoints of the study were the percentage change in body weight and the achievement of weight reduction of at least 5% at week 68 for oral semaglutide 50 mg compared to placebo. The trial assessed these endpoints regardless of treatment discontinuation or the use of other weight-lowering therapies (an intention-to-treat analysis).

The results demonstrated a meaningful difference in the percentage change in body weight between the two groups. The estimated mean bodyweight change from baseline (overall baseline value: 105.4 kg) to week 68 was -15.1% with oral semaglutide 50 mg compared to -2.4% with placebo, representing a significant estimated treatment difference of -12.7 percentage points (95% CI -14.2 to -11.3; p<0.0001). Further, a significantly greater number of participants achieved weight reductions of at least 5% (85% vs. 26%), 10% (69% vs. 12%), 15% (54% vs. 6%), and 20% (34% vs. 3%) at week 68 with oral semaglutide 50 mg compared to placebo.

“Having an oral formulation of semaglutide in addition to the subcutaneous, or injectable, formula available will allow people who struggle to lose weight with diet and physical activity alone to take this effective medication in a way that best suits them,” said Professor Filip K Knop MD, PhD, Gentofte Hospital, University of Copenhagen. “The weight loss also led to improvements in physical functioning, allowing participants to have an improved quality of life for everyday activities.”

OASIS 1 is the first trial in the OASIS clinical development program of oral semaglutide for the treatment of obesity. Other trials in the program will investigate its use in other populations (such as an East Asian population) and at a lower 25 mg dose.

Once-Daily Oral Semaglutide Shown to Improve Management of T2D

Findings from the PIONEER PLUS trial investigating the efficacy of higher investigational doses of once-daily oral semaglutide in adults with inadequately controlled T2D revealed promising results for treatment management with mean HbA1c reduction of up to 2·0% points. The trial was also simultaneously published in *The Lancet*.

This randomized, multicenter, double-blind, global phase 3b trial enrolled 1606 adults with T2D, HbA1c 8·0−10·5% (64−91 mmol/mol), a body-mass index of 25·0 kg/m2 or greater, receiving stable daily doses of 1–3 oral glucose-lowering drugs. Participants were randomly assigned to receive once-daily oral semaglutide at 14 mg, 25 mg, or 50 mg for 68 weeks. The primary endpoint was change in HbA1c from baseline to week 52. Safety was assessed in all participants who received at least one dose of the trial drug.

At baseline, mean HbA1c was 9·0% and mean body weight was 96.4 kg. Mean changes in HbA1c at week 52 were −1·5% points (standard error [SE] 0.05) with oral semaglutide 14 mg, −1·8% points (SE 0.06) with 25 mg, and −2·0% points (SE 0.06) with 50 mg. Weight loss of ≥5% and ≥10% also occurred more frequently in the 25 mg and 50 mg groups compared to the 14 mg group.

The safety profile of oral semaglutide 25 mg and 50 mg was consistent with the known profile of the GLP-1 receptor agonist class. Adverse events were reported by 404 (76%), 422 (79%) and 428 (80%) of participants respectively in the oral semaglutide 14 mg, 25 mg and 50 mg groups, respectively. Gastrointestinal disorders, which were mostly mild to moderate, occurred more frequently with oral semaglutide 25 mg and 50 mg than 14 mg.

“This trial provides compelling evidence that the availability of a wider range of doses of oral semaglutide will allow for individualized dosing to the desired effect, and the ability to intensify treatment as needed,” said Vanita R. Aroda, MD, of the Division of Endocrinology, Diabetes and Hypertension at Brigham and Women's Hospital, Boston, Massachusetts. “We are hopeful that these results encourage earlier effective management of type 2 diabetes and allow for broader management in the primary care setting.”

The authors of this study believe future real-world studies will be needed to investigate the clinical impact of the availability of higher doses of oral semaglutide.

Research presentation details:

Dr. Le Roux will present the findings at the following oral presentation session:

- Oral Presentations - Advances in Incretin Therapy

Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Finding Study of BI 456906 in People with Overweight/Obesity

- Presented on Friday, June 23, 2023 at 2:00 PM PST

Dr. Aroda and Professor Knop will present the findings at the following symposium:

- Symposium - Oral Semaglutide for Treatment of Obesity and Type 2 Diabetes—Results from OASIS 1 and PIONEER PLUS Trials
- Presented on Sunday, June 25, 2023 at 4:30 PM PST

About the ADA’s Scientific Sessions

The ADA's 83rd Scientific Sessions, the world's largest scientific meeting focused on diabetes research, prevention, and care, will be held in San Diego, CA on June 23–26. More than 12,000 leading physicians, scientists, and health care professionals from around the world are expected to convene both in person and virtually to unveil cutting-edge research, treatment recommendations, and advances toward a cure for diabetes. Attendees will receive exclusive

access to thousands of original research presentations and take part in provocative and engaging exchanges with leading diabetes experts. Join the Scientific Sessions conversation on social media using #ADA2023.

About the American Diabetes Association
The American Diabetes Association (ADA) is the nation's leading voluntary health organization fighting to bend the curve on the diabetes epidemic and help people living with diabetes thrive. For 82 years, the ADA has driven discovery and research to treat, manage, and prevent diabetes while working relentlessly for a cure. Through advocacy, program development, and education we aim to improve the quality of life for the over 133 million Americans living with diabetes or prediabetes. Diabetes has brought us together. What we do next will make us Connected for Life®. To learn more or to get involved, visit us at diabetes.org or call 1-800-DIABETES (1-800-342-2383). Join the fight with us on Facebook (American Diabetes Association), Spanish Facebook (Asociación Americana de la Diabetes), LinkedIn (American Diabetes Association), Twitter (@AmDiabetesAssn), and Instagram (@AmDiabetesAssn).

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