Oral semaglutide 7 mg and 14 mg doses showed superior reductions in blood sugar and weight compared to sitagliptin at 26 weeks in data presented at ENDO

New Orleans, US, 23 March 2019 – Oral semaglutide 7 mg and 14 mg demonstrated superior HbA1c and body weight reductions compared to Januvia® (sitagliptin 100 mg). Non-inferiority for oral semaglutide 3 mg for HbA1c reductions at 26 weeks was not confirmed. Presented today at the Endocrine Society Annual Meeting in New Orleans, Louisiana, with simultaneous publication in the Journal of the American Medical Association (JAMA)¹, PIONEER 3 was a phase 3a trial investigating the efficacy and long-term safety of oral semaglutide 3 mg, 7 mg and 14 mg compared with sitagliptin 100 mg in adults with type 2 diabetes inadequately controlled with metformin, with or without sulfonylurea, over 78 weeks. Oral semaglutide is an investigational once-daily glucagon-like peptide-1 (GLP-1) analogue in a pill.

“Many people living with type 2 diabetes do not meet their blood glucose targets despite many available oral antidiabetic therapies,” said Dr Dale Allison, PIONEER 3 investigator and director of medical research at the Hillcrest Family Health Center, Waco, Texas. “The PIONEER 3 findings are encouraging, as oral semaglutide demonstrated a clinically significant improvement in HbA1c and this investigational therapy has the potential to become the first oral GLP-1 receptor agonist for those living with type 2 diabetes.”

In PIONEER 3, the primary endpoints of HbA1c and confirmatory secondary endpoint of change in body weight were assessed after 26 weeks of treatment. When applying the primary statistical approach⁶, oral semaglutide 7 mg and 14 mg demonstrated superior HbA1c reductions of 1.0% and 1.3% at 26 weeks, compared to a 0.8% reduction with sitagliptin (both p<0.001). Oral semaglutide 3 mg demonstrated a reduction in HbA1c of 0.6%; non-inferiority compared to sitagliptin was not confirmed (p=0.09). Furthermore, at 26 weeks, oral semaglutide 7 mg and 14 mg demonstrated superior body weight reductions of 2.2 kg and 3.1 kg, both compared to a 0.6 kg reduction for sitagliptin (p<0.01).

¹ In PIONEER 3, two distinct statistical approaches were used to evaluate the effects of oral semaglutide. The primary statistical approach is known as the treatment policy (TPol) estimand and it was used to assess the effects of oral semaglutide regardless of discontinuation of trial product and/or use of rescue medication.
When applying the secondary statistical approach\(^b\) at week 26, oral semaglutide 7 mg and 14 mg demonstrated statistically significant reductions in HbA\(_{1c}\) of 1.1% and 1.4%, respectively, compared to a 0.8% reduction with sitagliptin (both p<0.001). Reductions in HbA\(_{1c}\) seen with oral semaglutide 3 mg were 0.5% and compared to the reductions seen with sitagliptin, the difference is statistically significant in favour of sitagliptin. Reductions in body weight from baseline were statistically significant in favour of all three oral semaglutide doses.

In a supportive secondary endpoint at week 78, oral semaglutide 14 mg demonstrated statistically significant reductions in HbA\(_{1c}\) compared to sitagliptin for both statistical approaches (1.1% vs 0.7%; p <0.001\(^a\); 1.1% vs 0.4%; p<0.001\(^b\)). There was no statistically significant difference with oral semaglutide 3 mg (both estimands) or 7 mg (TPol estimand) vs sitagliptin. Reductions in body weight from baseline, which was dose dependent, were statistically significant with oral semaglutide 3 mg, 7 mg and 14 mg at week 78 with reductions of 1.8 kg, 2.7 kg and 3.2 kg, respectively, compared to a 1.0 kg reduction with sitagliptin (all p<0.05\(^a\)) and 1.9 kg, 2.7 kg and 3.5 kg, respectively, compared to a 1.1 kg reduction with sitagliptin (all p<0.05\(^b\)).

In this 78-week trial, the most common adverse event for oral semaglutide was nausea, which was dose dependent, affecting 7.3% to 15.1%. The nausea rate for sitagliptin was 6.9%. People taking oral semaglutide 3 mg, 7 mg and 14 mg reported serious adverse events at a rate of 13.7%, 10.1% and 9.5%, respectively, compared to a rate of 12.4% of those taking sitagliptin. The proportion of people who discontinued treatment due to adverse events was 5.6%, 5.8% and 11.6% for people treated with oral semaglutide 3 mg, 7 mg and 14 mg, respectively, compared to 5.2% with sitagliptin.

**About PIONEER 3 and the PIONEER clinical trial programme**

PIONEER 3 was a 78-week, randomised, double-blind, double-dummy, active-controlled, parallel-group, multicentre, multinational trial with four arms comparing the efficacy and safety of oral semaglutide 3 mg, 7 mg and 14 mg with sitagliptin 100 mg in people with type 2 diabetes inadequately controlled with metformin, with or without sulfonylurea. PIONEER 3 randomised 1,864 people in a 1:1:1:1 manner to receive either a dose of oral semaglutide 3 mg, 7 mg and 14 mg or sitagliptin 100 mg once daily. The primary endpoint was change in HbA\(_{1c}\), and the confirmatory secondary endpoint was change in body weight, both from baseline to week 26.

The PIONEER phase 3a clinical development programme for oral semaglutide was a global development programme that enrolled 9,543 people with type 2 diabetes across 10 clinical trials. The programme was completed in 2018.

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\(^b\) The secondary statistical approach is known as the trial product estimand and it was used to assess the effect of oral semaglutide, assuming all patients remained on trial product and did not use rescue medication.
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