PIONEER 6

Key Points

- There is a Relative risk reduction of 21% in Major adverse cardiovascular events vs placebo.#
- The cardiovascular risk profile of oral semaglutide was non-inferior to placebo.

21% relative risk reduction in MACE*

49% reduction in all cause death

51% reduction in CV death

Problem

- Establishing cardiovascular safety of new therapies for type 2 diabetes is important. Safety data was available for the subcutaneous form of the glucagon-like peptide-1 receptor agonist semaglutide but was needed for oral semaglutide.

Objective

- To assess the cardiovascular (CV) safety of oral semaglutide among patients with type 2 diabetes.

Study Design

- An event-driven, randomized, double-blind, placebo-controlled trial involving patients at high cardiovascular risk (age of ≥ 50 years with established cardiovascular or moderate [stage 3] chronic kidney disease [CKD], or being aged ≥ 60 years with ≥ 1 other CV risk factor). The trial was conducted at 214 sites in 21 countries.
- Eligible patients were randomized in a 1:1 ratio to once - daily treatment with either oral semaglutide or placebo added to standard of care; with randomization stratified based on evidence of established CVD/moderate CKD at screening or CV risk factors only.
- The primary composite endpoint was time to first occurrence of CV death or non-fatal myocardial infarction or non-fatal stroke (MACE events).
- The primary hypothesis was to exclude an excess in CV risk with oral semaglutide by assessing non-inferiority versus placebo for the primary endpoint.
- PIONEER 6 was event- driven, with follow - up continued until accrual of at least 122 primary outcome events. There was pre-defined minimal duration.

Results

- Total 3183 patients were randomized to treatment. A maximum of 650 patients (approximately 20%) was permitted within the CV risk factors only stratum to ensure sufficient CV risk within the trial population to accrue enough events.
- 85% of patients in the oral semaglutide arm and 90% in the placebo arm were on-treatment at end of trial; 76 events were seen in the placebo group compared to 61 in the oral semaglutide group.
- The hazard ratio for oral semaglutide vs the placebo group was 0.79 (95% CI) with 21% relative risk reduction of MACE for non inferiority.
- PIONEER 6 was powered to test for non-inferiority, and this primary endpoint was statistically significant for non inferiority of oral semaglutide compared to placebo with a P-value of less than 0.0001.

Conclusion

- Oral semaglutide is non-inferior to placebo in terms of cardiovascular safety in patients with T2D and high cardiovascular risk, with established cardiovascular or chronic kidney disease.

For the use of a registered medical practitioner, hospital or laboratory only.
#Non significant
*non-significant for superiority, significant for non-inferiority
Reference: Husain, M., et al., Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med, 2019. 381(9): p. 841-851.

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