Subject: Competitive Intelligence - FLOW Trial (semaglutide)
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Metsera Reports

March 5, 2024

Clinical Trial Updates

Novo Nordisk announces 24% reduction in kidney/cardiac events in patients with CKD and T2DM

Summary and Implications

- The 24% relative risk reduction in the composite endpoint establishes the clinical utility of semaglutide in patients with CKD and T2DM, expanding the value narrative to this high prevalence, high need population
- FLOW is the first dedicated GLP-1RA study in CKD and T2DM
- Based on this data, Novo Nordisk will file for regulatory approval of a label expansion for Ozempic in US and EU

Context

Flow is among the many trials Novo is conducting to establish the clinical value of semaglutide in patients with T2DM and obesity who also have comorbid diseases. Novo announced on October 10, 2023 that it would stop FLOW trial early due to efficacy, based on a recommendation by the Independent Data Monitoring Committee.

CKD represents a large segment of overall T2DM population. Approximately 30-40% of T2DM patients have CKD. Prior studies with GLP-1RAs showed mixed results and were not powered to

demonstrate benefit in this subpopulation.

The effect of GLP1R agonists on kidney is not fully understood, but could be a mix of glycemic control, weight loss, reduced blood pressure, and perhaps inflammation and oxidative stress but this is yet to be proven.

Content

Efficacy: Semaglutide 1.0 mg dose shows 24% risk reduction in kidney disease-related events compared to placebo. Primary endpoint is composite of 5 components measuring CKD progression and risk of kidney, cardiovascular mortality. Novo explicitly stated both CKD and CV components of primary endpoint contributed to overall risk reduction.

Novo has not disclosed which secondary endpoints or components of primary endpoint were met. Novo may provide additional details on Capital Markets Day this Thursday (March 7, 2024). Full results will be presented at an upcoming congress (ADA, ACC).

Safety: Semaglutide 1.0 mg dose was tolerated similarly to previous semaglutide trials. Concomitant use of GLP1R agonists with SGLT2 inhibitors or ACE inhibitors / ARBs was well tolerated over 3-5 year period

Study Design: 3,533 pts with T2DM (HbA1C $\leq$ 10%) and CKD were enrolled. Participants received semaglutide or placebo (1:1) for 3-5 years (trial started in 2019). Trial is event driven with pre-defined minimum number of renal endpoint events. 5 events include: (1) eGFR decline of 50% or greater from trial start, (2) eGFR < 15 mL / min / 1.73 m^2 (end stage renal disease), (3) chronic dialysis required, (4) death from kidney disease, (5) death from cardiovascular disease. Dose escalation was 0.25 mg x 4 weeks, 0.5 mg x 4 weeks, and 1.0 mg thereafter. Participants must be previously treated with ACE inhibitor or ARB.

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