**Pancreatic Society of Great Britain and Ireland**

**Title:** Treatment with Volanesorsen (VLN) Reduced Triglycerides and Pancreatitis in Patients with Familial Chylomicronemia Syndrome (FCS) and Severe Hypertriglyceridemia (sHTG) vs Placebo: Results of the APPROACH and COMPASS Studies

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**Aim:** To evaluate if VLN, an antisense inhibitor of apoC-III, reduced pancreatitis in patients with FCS and severe HTG (sHTG) participating in two Phase 3 trials. FCS is a rare genetic disease characterized by severe chylomicronemia, sHTG and consequent risk of potentially fatal recurrent and acute pancreatitis (AP). HTG-induced AP has a more severe course, leading to worse outcomes.

**Methods:** The APPROACH study included 66 FCS patients with fasting TGs ≥8.4 mmol/L randomized 1:1 to 52 weeks of wkly VLN (300mg) or placebo (PBO). The COMPASS study included 113 sHTG patients with fasting TG ≥ 5.7 mmol/L randomized 2:1 to VLN or PBO wkly for 26 weeks. Endpoints included percentage reduction in plasma TGs at 13 weeks and treatment-emergent pancreatitis.

**Results**: Results from COMPASS & APPROACH combined showed a significant reduction (p=0.0185) in pancreatitis (1event in 1 patient in VLN group; 9 events in 6 patients in PBO group). Also, in APPROACH, patients with ≥2 episodes of pancreatitis in the 5 years before randomization suffered no attacks in the study treatment period (p=0.02).  In APPROACH, TGs at month 3 decreased by 77% in VLN group (n=33) and increased by 18% in PBO group (n=33) (p<0.0001). In COMPASS, VLN decreased TG 73% (p<0.0001) (n=75) after 3 months, compared with 2% decrease in PBO (n=38). The most common AE with VLN was injection site reaction (percentage of injections affected: 12% FCS/24% sHTG). Declines in platelet counts led to 5 early terminations in APPROACH, 2 of which had platelets <25,000/µl; platelet counts recovered to normal after VLN stopped. There were no serious platelet events in COMPASS, but 1 potentially related SAE reported as serum sickness occurred 2 weeks after the last study dose.

**Conclusions**: Volanesorsen treatment reduced TGs and consequent AP risk in FCS and sHTG patients.

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