A structurally engineered fatty acid, icosabutate, rapidly normalises elevated plasma ALT and gamma-glutamyl transferase (GGT) concentrations at a study population at high risk for NAFLD/NASH

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Introduction
• Excessive plasma and mitochondrial membrane polyunsaturated fatty acid peroxidation contributes to the pathology of steatohepatitis.
• We have recently shown that icosabutate (a structurally engineered EPA derivative that avoids membrane incorporation) markedly reduces fibrosis, hepatic oxidative stress and plasma alanine aminotransferase (ALT) in rodent models of NASH.
• Normalisation of plasma ALT is independently associated with histological improvements in NASH (1) whilst plasma gamma-glutamyltransferase (GGT) serves as a surrogate marker of cellular oxidative stress (2).
• To assess the potential translatability of the rodent findings to humans, we assessed time course changes in abnormal baseline ALT and GGT levels from 3 clinical trials in subjects with a high risk of NASH (hyperlipidemic, overweight/obese, high prevalence of diabetes) treated for up to 12 weeks with oral icosabutate (600mg q.d) or placebo.

Methods
• Subjects with abnormal baseline ALT (>40 U/L) or GGT (>38 U/L females, >51 U/L males) from 3 clinical trials with icosabutate were identified.
• Plasma ALT and GGT were assessed over 5 time points: baseline, 1, 2, 3 and 4 weeks (study end) in NCT02364625 (phase 1b) and baseline, 2, 4, 8 and 12 weeks (study end) in NCT01972178 (both phase 2a studies, see references 3 and 4).
• Sequential time points were characterized as baseline, 1-1, 2-3, 3-4d and differences versus baseline were assessed via Friedman's ANOVA with Dunn's correction.

Results
Effects of icosabutate on hepatic oxidative stress, ALT and fibrosis in rodents

Changes in plasma and HOMA-IR in the total study population

Pre-treatment (baseline) characteristics of the study population

Conclusion
• Oral icosabutate (600mg d.) reduces elevated liver enzymes within 1-2 weeks in a patient population with a high prevalence of NASH, with >80% of subjects achieving normal ALT and/or GGT levels within 12 weeks.
• Absolute decreases in ALT are comparable/superior to those that have been associated with histological responses in NASH intervention trials.
• Robust GGT decreases in line with potent hepatic antioxidant effect seen in multiple NASH mouse models.
• An upcoming 12 month phase 2b trial (ICONA) with icosabutate will confirm whether reductions in liver enzymes in a study population with a high prevalence of NAFLD/NASH are also predictive of decreases in fibrosis and inflammation in patients with biopsy-confirmed NASH.

References