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

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Introduction

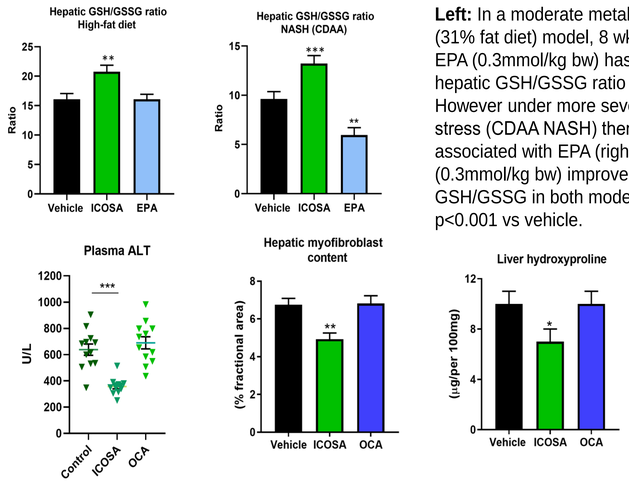
- Excessive plasma and mitochondrial membrane polyunsaturated fatty acid peroxidation contributes to the pathology of steatohepatitis.
- We have recently shown that icosabutate (a structurally engineered EPA derivative that avoids membrane incorporation) markedly reduces fibrosis, hepatic oxidative stress 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 NCT02364635 (phase 1b) and baseline, 2, 4, 8 and 12 weeks (study end) in NCT01893515 and NCT01972178 (both phase 2a studies, see references 3 and 4).
- Sequential time points were characterized as baseline, t=1, t=2, t=3 and t=4 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



Left: In a moderate metabolic overload (31% fat diet) model, 8 wks feeding with EPA (0.3mmol/kg bw) has no effect upon hepatic GSH/GSSG ratio (far left). However under more severe hepatic stress (CDAA NASH) there's a marked fall associated with EPA (right). Icosabutate (0.3mmol/kg bw) improves hepatic GSH/GSSG in both models. **p<0.01, p<0.001 vs vehicle.

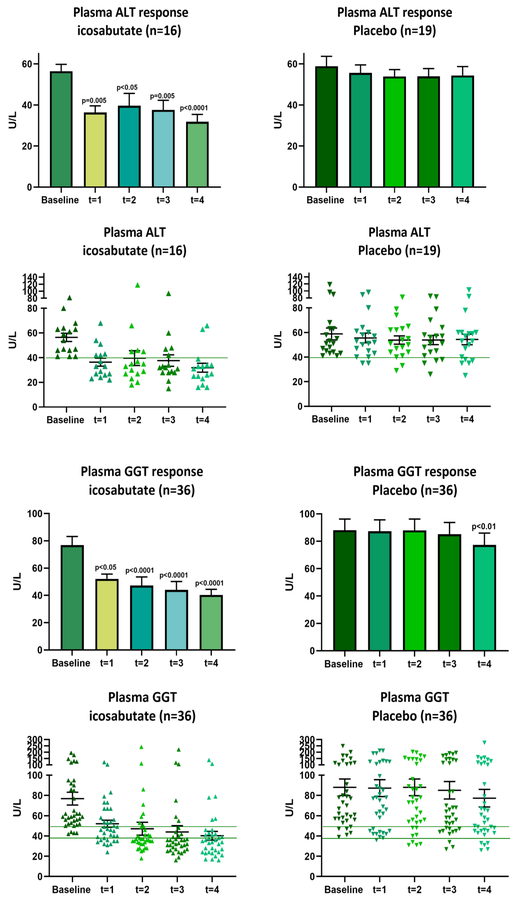
Above: In an *ob/ob*-NASH model, icosabutate, but not obeticholic acid (OCA) decreases plasma ALT, hepatic myofibroblast (α-SMA) and collagen content. *p<0.05, **p<0.01, ***p<0.001 vs vehicle.

Pre-treatment (baseline) characteristics of the total study population

	Phase 1b: Hypercholesterolemia NCT02364635		Phase 2: Mixed dyslipidemia NCT01972178		Phase 2: Severe HTG NCT01893515	
	Icosabutate (n=18)	Placebo (n=6)	Icosabutate (n=56)	Placebo (n=57)	Icosabutate (n=43)	Placebo (n=44)
Age (mean)	56	51	58.7	58	53.5	51.6
BMI (mean)	28.1	27.3	31.5	31.7	31.7	32.3
Diabetes (%)	17	17	34	25	41.8	38.6
On statin (%)	100*	100*	100	100	20.5	20.9
Plasma TG (mg/dl)	136**	192**	270	256	610	687
Non-HDL-C (mg/dl)	180**	205**	166	163	226	207

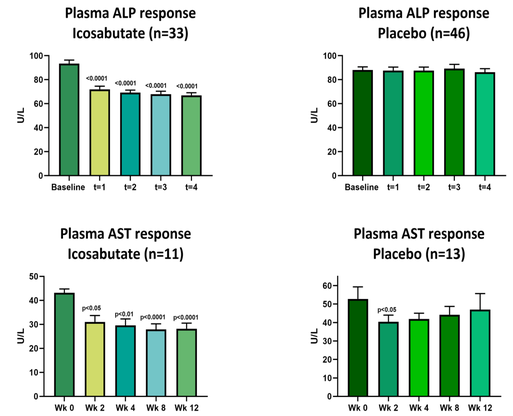
**All subjects were taken off statins 4-weeks prior to treatment with icosabutate for phase 1b*
***Lipid values are median except phase 1b (geometric mean)*

Changes in elevated baseline liver enzymes in response to icosabutate 600mg/d



Left: 45% reduction in mean plasma ALT (56 baseline vs 31 U/L study end) in response to icosabutate with 14/16 subjects achieving a normal ALT at study end vs 5/19 in placebo. Horizontal line represents abnormal threshold.

Left: Icosabutate reduced mean plasma GGT by 48% (77 baseline vs 40 U/L study end) with 81% (29/36) subjects achieving a normal GGT at study end vs 25% (9/36) in the icosabutate and placebo groups respectively. Horizontal lines represents abnormal threshold (male upper).



Left. Changes in plasma ALP and AST. The ALP threshold was lowered to >70U/L to capture sufficient subjects as few were above the protocol specified >107U/L threshold. Both ALP and AST were significantly reduced at all time-points in icosabutate treated subjects.

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

	Phase 1b: Hypercholesterolemia (taken off statins)		Phase 2: Mixed dyslipidemia on statin (Ref 4)		Phase 2: Severe HTG (Ref 3)	
	Icosabutate	Placebo	Icosabutate	Placebo	Icosabutate	Placebo
Plasma TG (mg/dl) baseline	136	192	270	256	610	687
Plasma TG (mg/dl) week 12	82**	173	156***	236	314***	590
Non-HDL-C (mg/dl) baseline	180	205	162.5	165.5	226	207
Non-HDL-C (mg/dl) week 12	117***	200	149	163	195	189
HOMA-IR baseline	-	-	4.1	4.3	6.7	7.2
HOMA-IR week 12	-	-	4	4.5	4.3**	6.8

Values are median except phase 1b (geometric means). See references 3 & 4 for complete data sets. **p≤0.01, ***p<0.0001 vs placebo

Conclusion

- Oral icosabutate (600mg q.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

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General hepatology
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