ICOSABUTATE, A NOVEL ORAL FREE FATTY ACID RECEPTOR AGONIST, SIGNIFICANTLY DECREASES BIOMARKERS OF NASH AND FIBROSIS INDEPENDENT OF BASELINE FIBROSIS AND INFLAMMATION

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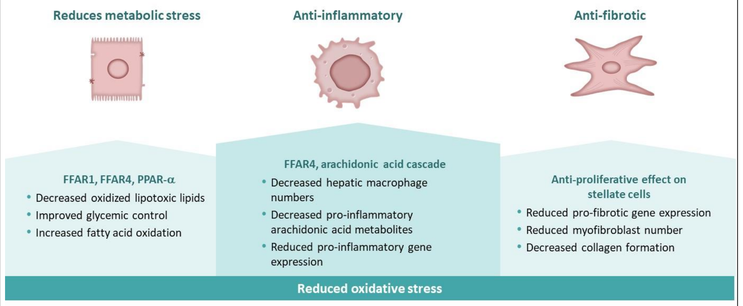
INTRODUCTION

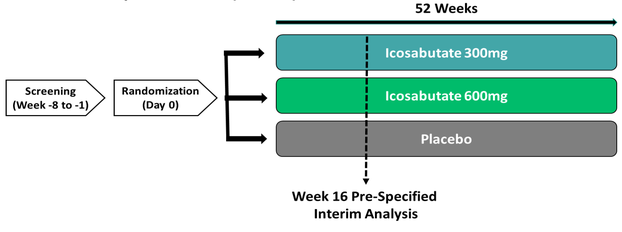
- Icosabutate (ICOSA) is an oral, liver-targeted engineered fatty acid with potent anti-inflammatory and antifibrotic activity in animal models and pleiotropic beneficial effects in patients with lipid disorders
- ICOSA is a full free fatty acid receptor 4 (FFAR4) agonist, a receptor highly expressed in Kupffer cells with potent anti-inflammatory activity
- Signaling via other pathways (PPAR-α and arachidonic acid cascade) further contribute to the anti-inflammatory and anti-fibrotic activity



- The ICONA trial is an ongoing 52-week, multicenter, placebo-controlled, phase 2b study enrolling 264 subjects with biopsy confirmed NASH.
- All subjects had stage 1-3 fibrosis, NAS ≥4 (1 point in each component) and ≥10% liver fat content by MRI-PDFF.
- A prespecified interim analysis was performed evaluating multiple non-invasive biomarkers relevant for NASH and fibrosis.
- We present a post-hoc analysis in a subset of patients with more severe disease as defined by histology or biomarkers of inflammation and fibrosis.

METHODS

- A total of 99 subjects were randomized (1:1:1) to ICOSA 300 or 600 mg or placebo and treated through Week 16.
- The severe disease sub-populations analyzed included cohorts of patients with F2/F3 fibrosis (66% of total), ALT >60 U/L (44% of total), Pro-C3 > 15.5 ng/ml (62% of total) or hsCRP >3.0 mg/L (67% of total) at baseline.
- Treatment response was assessed by fibrosis stage or disease severity thresholds of each biomarker and compared to the overall population.
- Placebo-adjusted treatment responses were analyzed using an ANCOVA model and reported as Least-Square Means (95% CI).

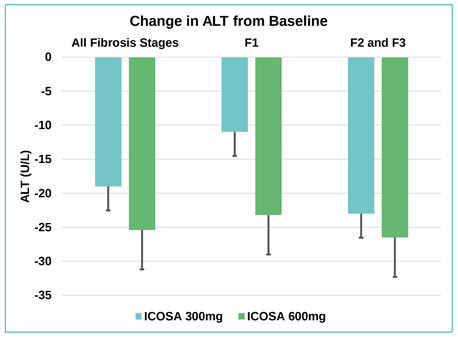


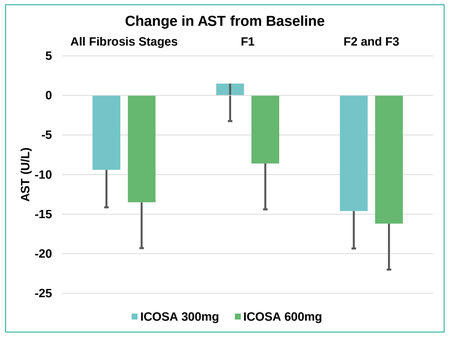
BASELINE PATIENT AND DISEASE CHARACTERISTICS

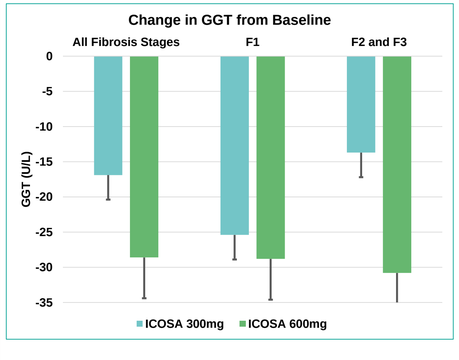
Parameter	Placebo (n=33)	ICOSA 300mg (n=33)	ICOSA 600mg (n=33)
Age (Y)	54 (22-75)	52.6 (28-73)	53.3 (29-71)
Female/Male	75.6% / 24.4%	62.2% / 37.8%	70.5% / 29.5%
White (%)	95.6%	90.9%	90.9%
Hispanic/Latino (%)	42.0%	38.6%	31.8%
Weight (kg)	95.4 (20.3)	103.7 (19.2)	101.3 (18.9)
F1 / F2+F3 (%)	36% / 64%	30% / 70%	36% / 64%
ALT (U/L)	65.3 (37.9)	67.7 (37.0)	64.4 (36.2)
AST (U/L)	49.3 (30.3)	52.2 (32.3)	42.2 (17.8)
GGT (U/L)	72.5 (62.2)	85.2 (64.2)	78.5 (103.9)
Triglycerides (mg/dL)	152.3 (62.5)	175.8 (96.4)	199.2 (113.7)
PRO-C3 (ng/mL)	19.2 (9.9)	18.9 (7.1)	18.4 (5.3)
MRI-cT1 (ms)	984.3 (178.1)	1022.1 (160.9)	980.5 (126.0)
MRI-PDFF (%)	21.1 (8.9)	20.8 (6.3)	20.5 (5.9)

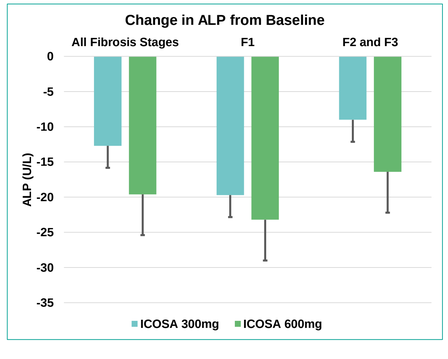
RESULTS

Changes in Liver Enzymes by Fibrosis Stage

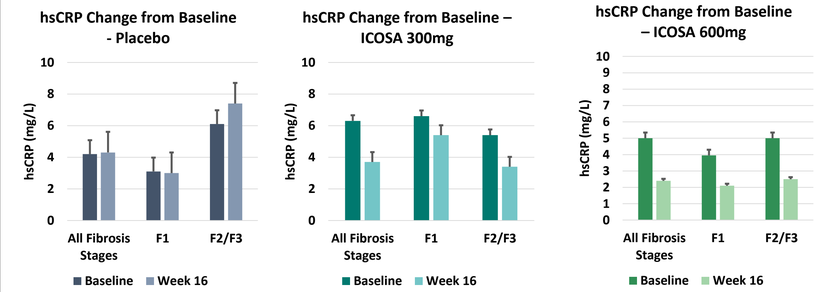








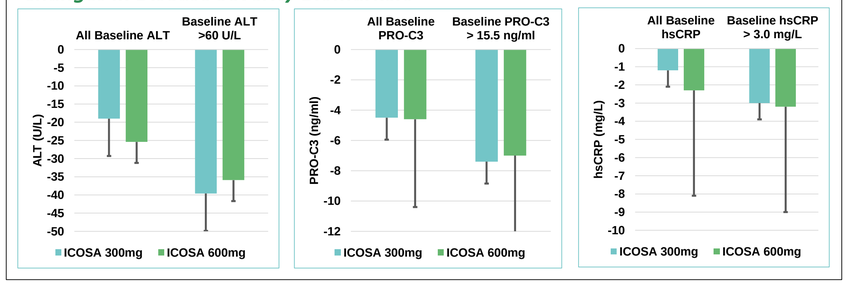
Changes in Biomarkers of Inflammation by Fibrosis Stage



Changes in Fibrosis Biomarkers by Fibrosis Stage

Parameter	ICOSA 300 mg			ICOSA 600mg		
	Overall	F1	F2/F3	Overall	F1	F2/F3
PRO-C3 (ng/ml)	-4.5	-4.1	-4.6	-4.6	-3.0	-5.4
ELF	-0.41	-0.35	-0.37	-0.54	-0.60	-0.47
PIINP	-2.7	-2.6	-2.8	-3.0	-2.3	-3.3
TIMP-1	-14.0	-21.9	-9.8	-23.6	-29.4	-20.6
Hyaluronic Acid	-35.1	-21.7	-37.8	-34.1	-31.1	-34.7

Changes in Disease Severity Biomarkers



CONCLUSIONS

- Rapid and sustained significant decreases were seen in F2/F3 patients in all biomarkers at 600mg and the majority at 300mg that were largely comparable or of greater magnitude than the overall study population
- Improvements in key markers associated with disease severity demonstrate the potent anti-inflammatory and anti-fibrogenic activity of ICOSA
- These data are supportive of a potential impact on liver histology at 52 weeks across a broad range of patients, largely independent of baseline fibrosis or inflammation.
- Based on the clinical data generated to date, along with a favorable safety and tolerability profile, ICOSA has the potential to be a backbone for either mono- or combination therapy in NASH.

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