Icosabutate, a novel structurally engineered fatty acid, significantly reduces relevant markers of NASH and fibrosis in 16 weeks: Results of an interim analysis of the Phase 2b ICONA trial

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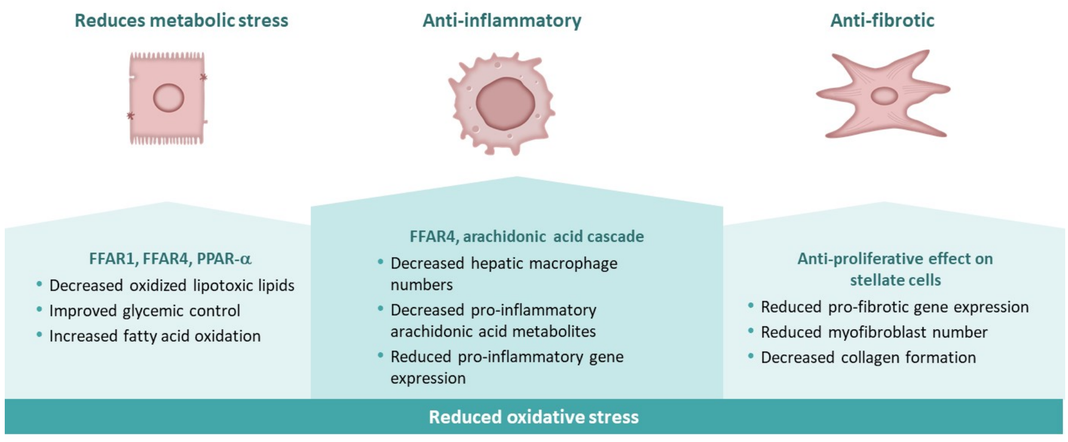
Introduction

- Icosabutate (ICOSA) is an oral, liver-targeted engineered fatty acid with potent anti-inflammatory and antifibrotic activity in animal models and marked effects in patients with lipid disorders
- ICOSA is a full free fatty acid receptor 4 (FFAR4) β-arrestin2 agonist which inhibits multiple pro-inflammatory cascades
- Signaling via other pathways (PPAR-α and arachidonic acid cascade) further contribute to the anti-inflammatory and anti-fibrotic activity

Figure 1. Icosabutate Mechanism of Action

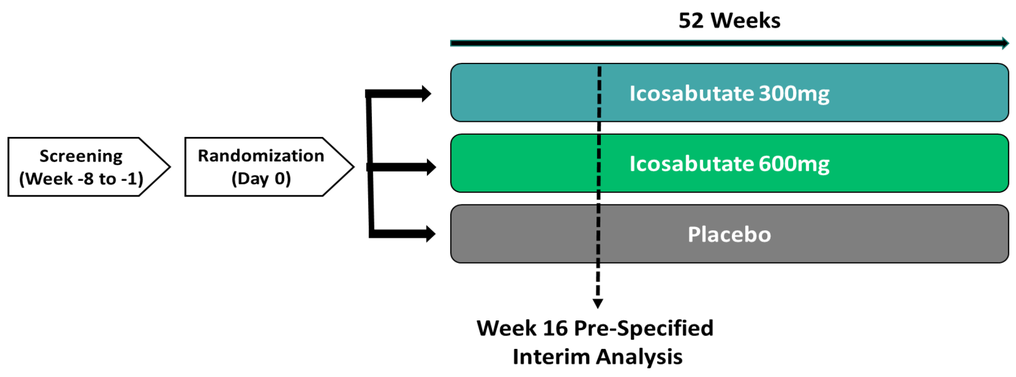


- The ICONA trial is an ongoing 52-week, multicenter, placebo-controlled, Phase 2b study enrolling 264 subjects with biopsy confirmed NASH
- We present the results of a prespecified interim analysis at Week 16 in the first 90 randomized participants evaluating multiple non-invasive biomarkers relevant for NASH, fibrosis, metabolic syndrome, lipid metabolism and cardiovascular risk

Methods

- Ninety participants were randomized (1:1:1) to oral capsules of ICOSA 300 mg or 600 mg versus placebo once daily and treated for 16 out of the 52 weeks
- The primary endpoint is resolution of NASH with no worsening of fibrosis as defined by the NASH CRN at Week 52
- Key histologic and imaging inclusion criteria include biopsy-proven NASH, NAS ≥4 (with 1 point in each component), stage 1-3 fibrosis and ≥ 10% liver fat by MRI-PDFF.
- The prespecified hierarchal interim analysis evaluated key parameters ranked in order of importance to ICOSA mechanism of action: ALT, GGT, triglycerides, Pro-C3, MRI-cT1 and MRI-PDFF

Figure 2. ICONA Trial Study Design



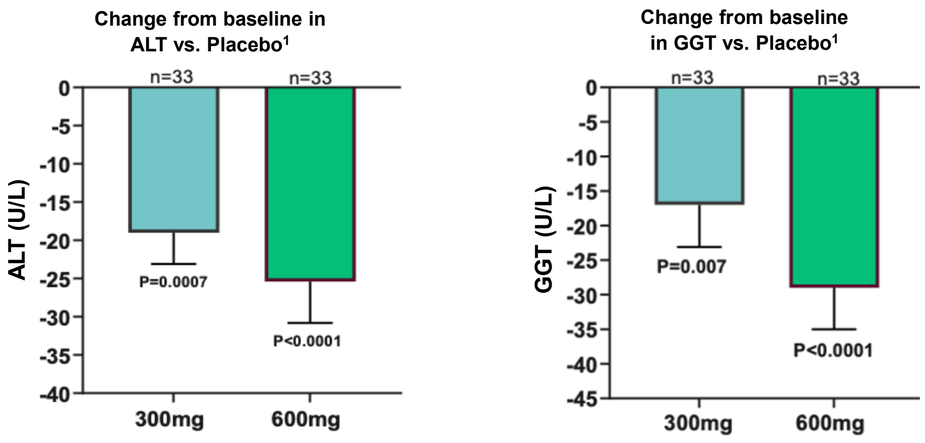
Results

Baseline Patient and Disease Characteristics

Parameter	Placebo	ICOSA 300mg	ICOSA 600mg
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)
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)

Continuous parameters presented as Mean (SD)

Liver Enzymes

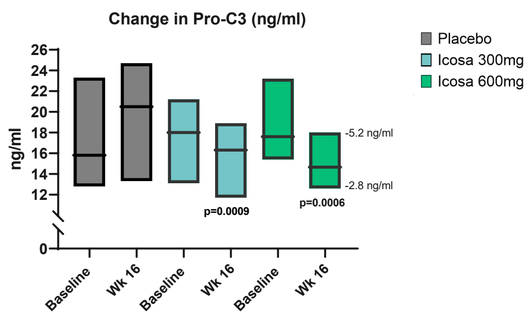


Parameter	ICOSA 300 mg Change vs. Placebo[1]	ICOSA 600 mg Change vs. Placebo[1]
AST (U/L)	-10.2 (-19,-1.4)#	-14.7 (-23.7, -5.7)*
ALP (U/L)	-12.7 (-17.4, -7.9)*	-19.6 (-24.4, -14.9)*
Total Bilirubin (mg/dL)	0.0 (-0.1, 0.1)	-0.14 (-0.23, -0.06)#

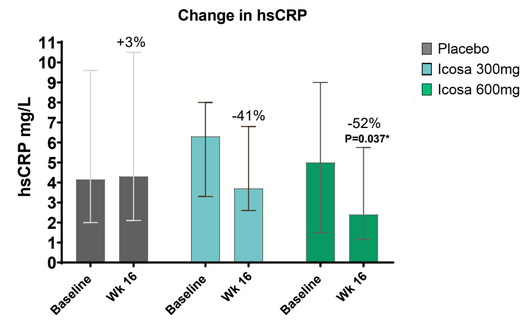
[1] LS means (95% CI) **p< 0.001 #p<0.05*

Results (cont'd)

Fibrogenesis and Inflammation Biomarkers



Median (Q1, Q3) values. P-value = LS mean change vs placebo

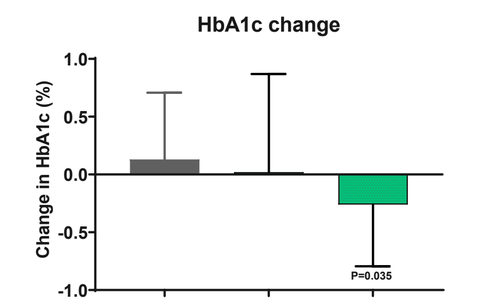


Median (Q1, Q3) values shown, P-value vs. placebo

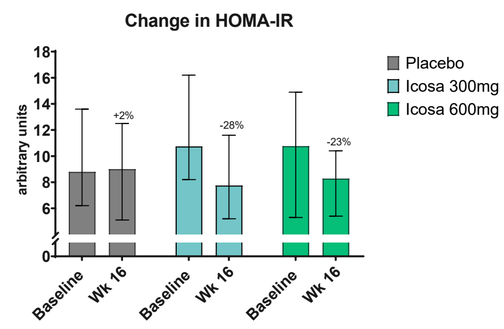
Parameter	ICOSA 300 mg Change vs. Placebo[1]	ICOSA 600 mg Change vs. Placebo[1]
Total ELF Score	-0.4 (-0.7, -0.1)#	-0.5 (-0.8, -0.3)*
PIIINP	-2.7 (-4.4, -1.0)#	-3.0 (-4.6, -1.3)*
TIMP-1	-14.0 (-35.7, -7.7)	-23.6 (-45.4, -1.8)#
Hyaluronic Acid	-35.1 (-65.8, -4.3)#	-34.1 (-64.1, -4.1)#

[1] LS means (95% CI) *P< 0.001 #P<0.05

Metabolic and Lipid Parameters



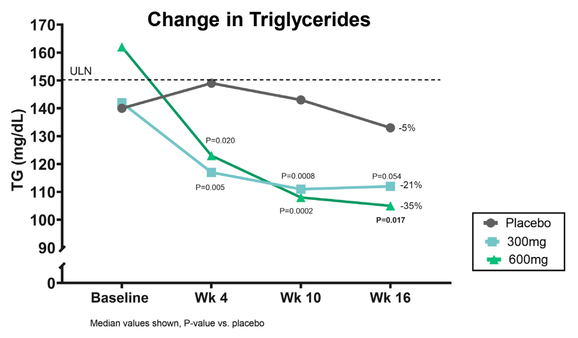
Excludes subjects who received prohibited medication (P=0.060 for all subjects)
P-value vs. placebo



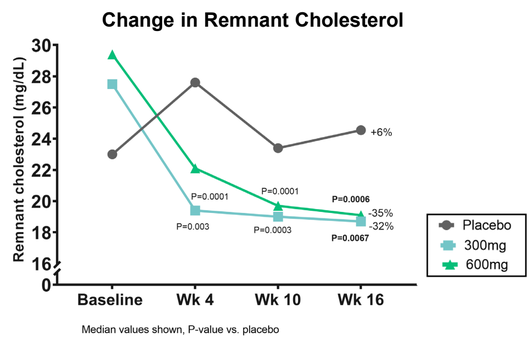
Median (Q1, Q3) values

Parameter	ICOSA 300 mg Change vs. Placebo [1]	ICOSA 600 mg Change vs. Placebo [1]
Triglycerides(mg/dL)	-27.1 (-54.6, 0.5)	-34.0 (-61.9, -6.1)#
LDL-C (mg/dL)	5.5 (-5.5, 16.6)	-3.9 (-14.9, 7.1)
HDL-C (mg/dL)	3.2 (0.0, 6.3)	2.3 (-0.9, 5.4)
Total Cholesterol (mg/dL)	2.5 (-9.2, 7.5)	-9.5 (-9.5, -15.1, 1.5)
ApoB (mg/dL)	-0.8 (-9.2, 7.5)	-6.8 (-15.1, 1.5)
Remnant-C (mg/dL)	-6.1 (-10.5, -1.8)#	-8 (-12.5, -3.6)*
ApoC3 (mg/dL)	-1.6 (-3.0, -0.2)	-2.7 (-4.1, -1.3)*
Lipoprotein-a (mmol/L)	-5.2 (-11.2 , 0.9)	1.5 (-4.6, 7.5)

[1] LS means (95% CI) *p< 0.001 #p<0.05



Median values shown, P-value vs. placebo



Median values shown, P-value vs. placebo

Safety and Tolerability

- A blinded, safety review across all study arms was performed
- There was no difference in the TEAE severity or causality in ICOSA vs placebo-treated participants during the 16-week IA study period
- The most common TEAEs (>5%) observed across the study arms were diarrhea and nausea, the majority of which were mild and unrelated to study drug.
- No drug-induced liver injury, cardiovascular events, or worsening of diabetes were observed during the treatment period
- No increase in weight or BMI was seen during the study period
- Laboratory values remained stable or improved and there were no clinically relevant changes in vital signs or ECGs
- No safety or tolerability signals of concern were observed during the study period as confirmed by an independent unblinded Data Safety Monitoring Committee review

	Placebo	Icosabutate 300mg	Icosabutate 600 mg
Any TEAE	37 (80.4%)	30 (65.2%)	37 (78.75)
Maximum Severity			
Grade 1	12 (26.1%)	7 (15.2%)	9 (19.1%)
Grade 2	24 (52.2%)	22 (47.8%)	20 (42.6%)
Grade 3	1 (2.2%)	1 (2.2%)	4 (8.5%)
Grade 4	0	0	0
Grade 5	0	0	0
Drug Related TEAE	7 (15.2%)	7 (15.2%)	8 (17%)
SAE	1 (2.2%)	1 (2.2%)	3 (6.4%)
Related SAE	0	0	0

Conclusions

- Treatment with ICOSA for 16 weeks resulted in rapid and sustained decreases in markers of liver injury, inflammation and fibrogenesis along with improvements in glycemic control and atherogenic lipids in patients with biopsy-confirmed NASH
- These data support a potential for ICOSA to impact liver histology at 52 weeks as well as improving common comorbid conditions seen in NASH patients
- A favorable safety and tolerability profile was observed in ICOSA treated patients, similar to placebo and consistent with prior studies in patients with lipid disorders
- Based on recent preclinical data and the clinical data generated to date, ICOSA has the potential to be a backbone for either mono- or combination therapy in NASH

Acknowledgement: We are immensely grateful for the patients participating in the ICONA trial and the investigators for the successful conduct of the trial