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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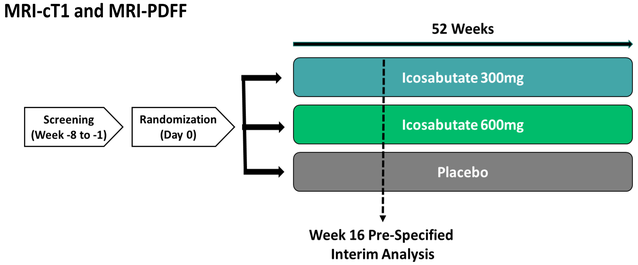
Introduction

- Icosabutate (ICOSA) is an oral, liver-targeted GPR-120 (free fatty acid receptor 4) agonist with potent anti-inflammatory activity in animal models and patients with lipid disorders
- 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 are 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



Baseline Patient and Disease Characteristics

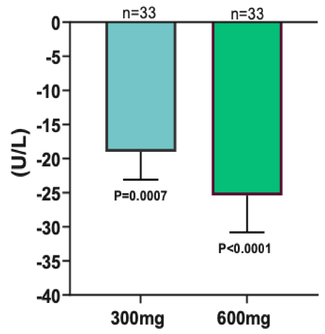
Parameter	Placebo	ICOSA 300mg	ICOSA 600mg
Age (Y)	54 (22-75)	52.6 (28-73)	53.3 (29-71)
Female/Male	75.6% / 24.4%	62.2% / 37.8%	70.5% / 29.5%
White (%)	95.6%	90.9%	90.9%
Hispanic/Latino (%)	42.0%	38.6%	31.8%
Weight (kg)	95.4 (20.3)	103.7 (19.2)	101.3 (18.9)
ALT (U/L)	65.3 (37.9)	67.7 (37.0)	64.4 (36.2)
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)

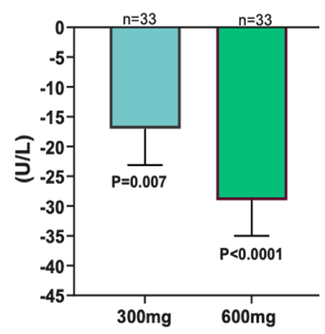
Results

Liver Enzymes

Change from baseline in ALT vs. Placebo[1]



Change from baseline in GGT vs. Placebo[1]

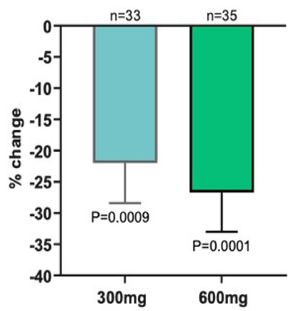


Parameter	ICOSA 300 mg Change vs. Placebo[1]	ICOSA 600 mg Change vs. Placebo[1]
AST (U/L)	-10.2 (-19,-1.4)#	-14.7 (-23.7, -5.7)*
ALP (U/L)	-12.7 (-17.4, -7.9)*	-19.6 (-24.4, -14.9)*
Total Bilirubin (mg/dL)	0.0 (-0.1, 0.1)	-0.14 (-0.23, -0.06)#

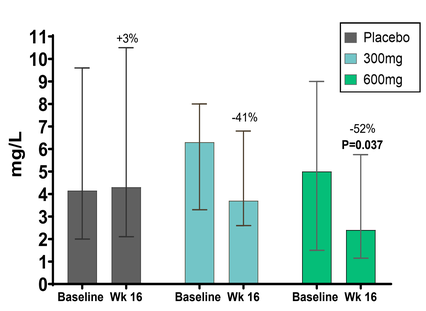
[1] *LS means (95% CI)* *p< 0.001 #p<0.05

Fibrogenesis and Inflammation Biomarkers

Change (%) in Pro-C3 vs. Placebo[1]



Change in hsCRP [1,2]



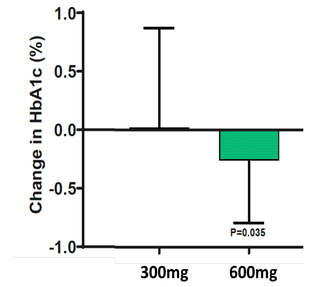
[1]*LS means (95% CI),* [2]*Median values (Q1, Q3)*

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)#

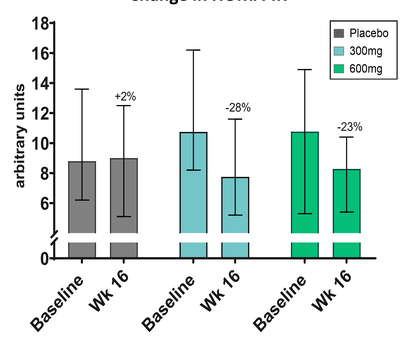
[1] *LS means (95% CI)* *p< 0.001 #p<0.05

Metabolic and Lipid Parameters

Change in HbA1c vs. Placebo[1]



Change in HOMA-IR [2]



[1] *LS means (95% CI),* [2]*Median values (Q1,Q3)*

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

Safety and Tolerability

- A blinded, safety review across all study arms was performed as part of the interim analysis.
- 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
- 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

Conclusions

- Rapid and sustained decreases in markers of liver injury, inflammation and fibrogenesis along with improvements in glycemic control and atherogenic lipids were seen after treating NASH patients for 16-weeks with ICOSA
- These data support a potential for ICOSA to impacting liver histology at 52 weeks as well as improving common comorbid conditions seen in NASH patients
- Based on recent preclinical data (see Poster # 2006-PO) and the clinical data generated to date, ICOSA has the potential to be a backbone for either mono- or combination therapy in NASH