Treatment With BIO89-100 Led to Decreased Spleen Volume that was Correlated with Relative Change in Liver Fat Volume, CK-18 and Platelet count in a Phase 1b/2a, Placebo-controlled, Double-blind, NASH Proof of Concept Study

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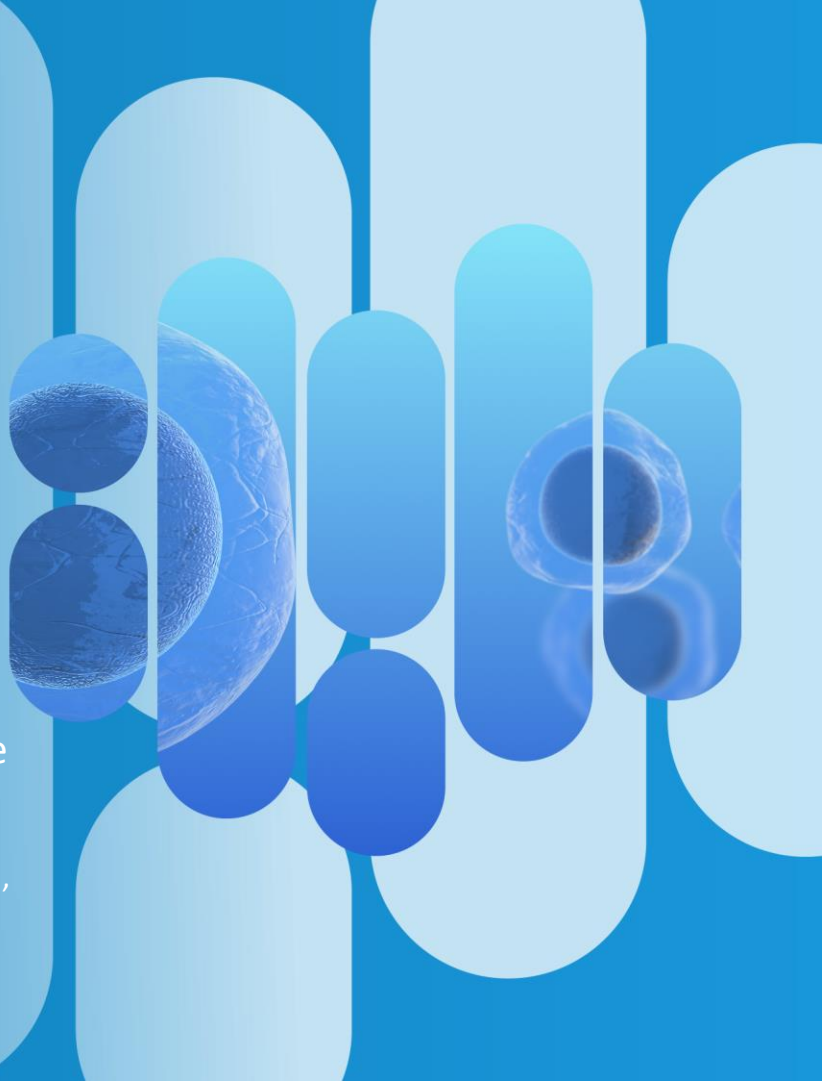

Disclosures

Rohit Loomba, MD, MHSc

I disclose the following financial relationship(s) with a commercial interest:

- Consultant: Aardvark Therapeutics, Altimmune, Anylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol-Myer Squibb, CohBar, Eli Lilly, Galmed, Gilead, Glympse bio, Hightide, Inipharma, Intercept, Inventiva, Ionis, Janssen Inc., Madrigal, Metacrine, Inc., NGM Biopharmaceuticals, Novartis, Novo Nordisk, Merck, Pfizer, Sagimet, Theratechnologies, 89 bio, Terns Pharmaceuticals and Viking Therapeutics.
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Background (1):

- FGF21 is an endogenous hormone regulating carbohydrate, lipid and energy metabolism. FGF21 analogs have demonstrated improvements in liver and metabolic abnormalities in NASH
- BIO89-100 is a glycoPEGylated FGF21 analog being developed for treatment of NASH
- In a phase 1b/2a POC study in subjects with NASH BIO89-100 led to significant reductions in liver fat by MRI-PDFF and volume by MRI, with concurrent metabolic benefits and a favorable safety and tolerability profile
- The aim of the post-hoc sub-study was to examine the effect of BIO89-100 vs placebo on spleen volume (SV) in subjects with NASH

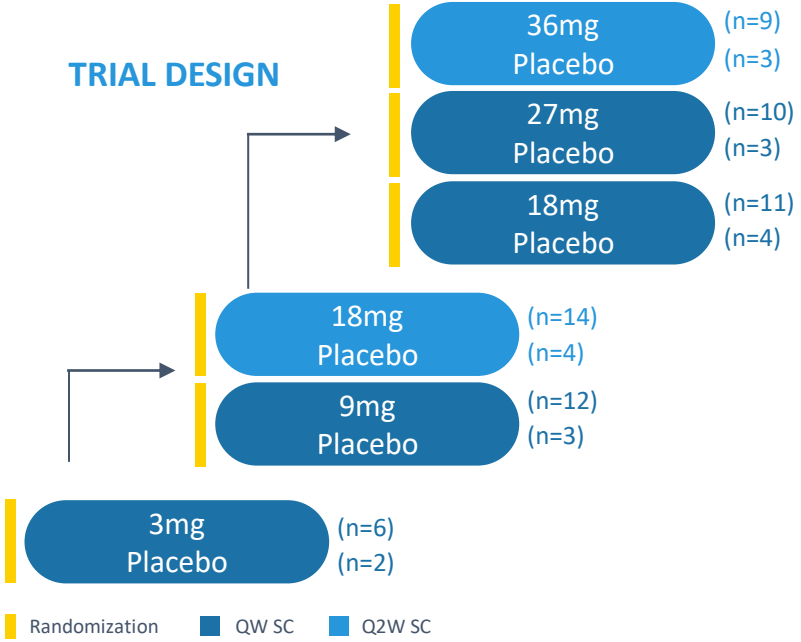
Background (2):

- Emerging data suggest spleen elastography may be helpful in detection of liver fibrosis stage and portal hypertension in patients with NAFLD
- A correlation between spleen elastography[1] and spleen volume (SV) assessments and hepatic venous pressure gradient has previously been demonstrated
- Association between changes in SV and improvement in NALFD have not been systematically assessed

[1] Colecchia A et al, *Gastroenterology* 2012; 143: 646.

BIO89-100-002 (NCT4048135): A Double Blind, Placebo Controlled, Multi-center, Phase 1b/2a study

TRIAL DESIGN



- 12-week treatment duration + 4-week safety follow up
- Placebo (n=19) combined across cohorts for analysis

KEY INCLUSION CRITERIA

- NASH* or phenotypic NASH (PNASH)#
- PDFF≥10%

*Subjects with biopsy-proven F1-3

#Central obesity plus T2DM or evidence of liver injury

KEY TRIAL ENDPOINTS

- Safety, PK
- Relative changes in liver fat
- Serum lipids, liver and metabolic markers

- Randomized, pharmacodynamic (PD) and safety analysis set n=81; Study completers n=71
- MRI analysis set n=75 (subjects with post-baseline MRI)

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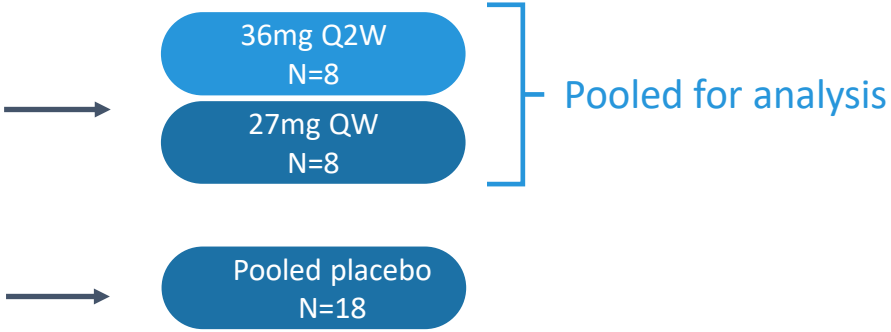
BIO89-100-002 (NCT4048135): Spleen Volume Post Hoc Analysis



- SV was assessed by MRI at Baseline, Day 50 and Day 92.
- Correlation of baseline SV and change in SV to various clinical and lab parameters was investigated

Baseline Characteristics

Characteristic	Placebo (N=18) Median [Range]	BIO89-100 (N=16) Median [Range]
Age (years)	56.5 [37.4, 66.3]	47.6 [37.7, 66.6]
Male gender (%)	38.9	56.3
T2DM (%)	61%	25%
BMI (kg/m^2)	33.5 [29.5, 39.8]	36.6 [28.8, 44.8]
ALT (U/L)	29 [14, 95]	53 [17, 178]
CK-18 (U/L)	113 [39, 1078]	179 [39, 1548]
Pro-C3 (ng/ml)	10.9 [3.05, 17.20]	15.7 [8.70, 20.30]
VCTE (kPa)	7.1 [2.9, 12.0]	8.0 [4.0, 11.4]
MRI-PDFF (%)	19.7 [10.5, 39.5]	19.3 [12.1, 41.1]
Liver volume (L)	2.1 [1.300, 2.830]	2.4 [1.503, 3.481]
Spleen volume (mL)*	170.9 [107.6, 366.9]	232.6 [137.6, 504.4]

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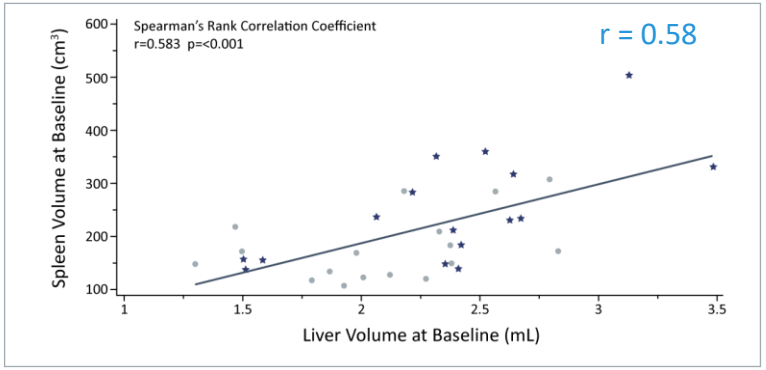
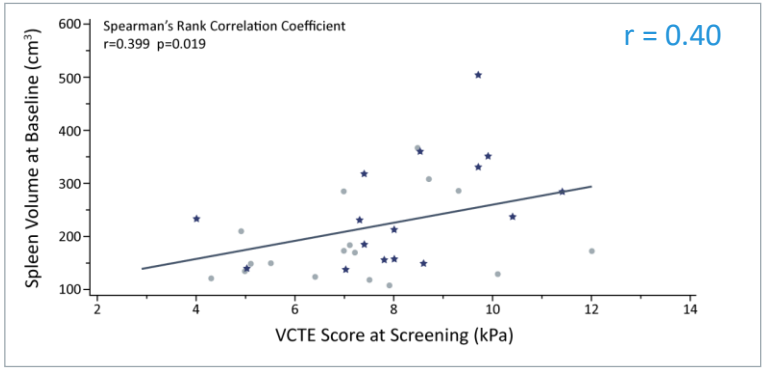
*Within normal range [Linguraru et al. *Acad Radiol* 2013; 20(6): 675].

Baseline Spleen Volume Correlates with Liver Volume, VCTE Score, BMI, and Platelet Count

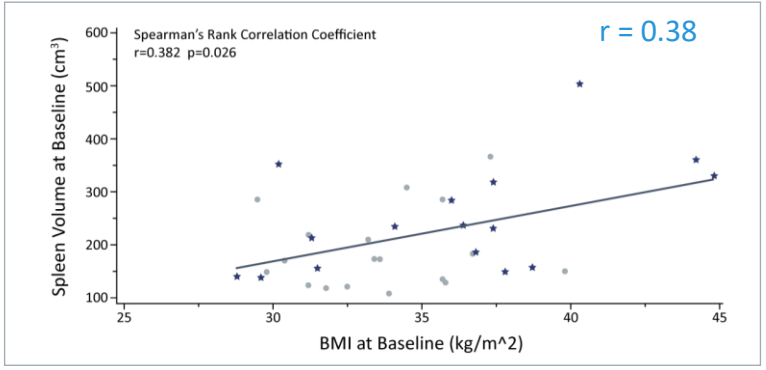
Liver Volume



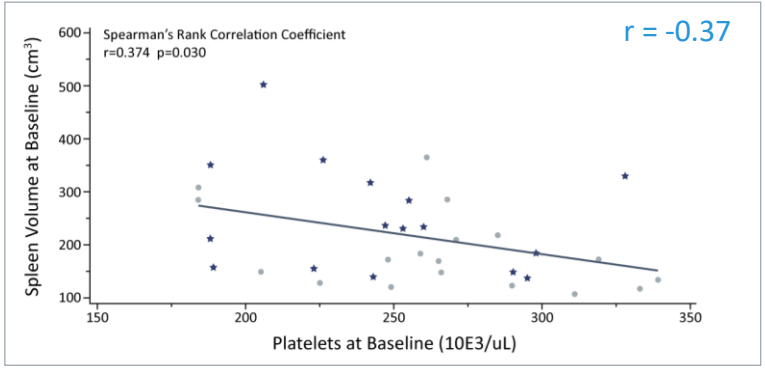
VCTE Score



BMI



Platelet Count



Placebo ★ BIO89-100 27mg + 36mg Q2W Pooled

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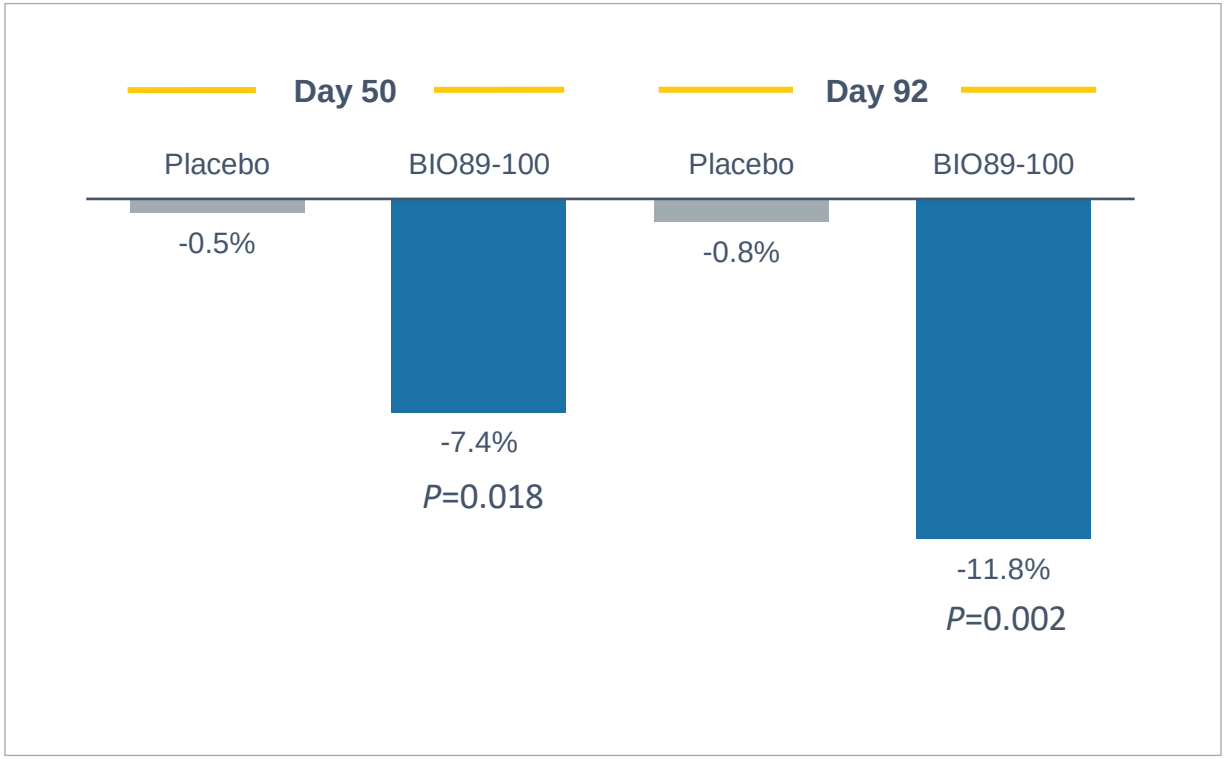
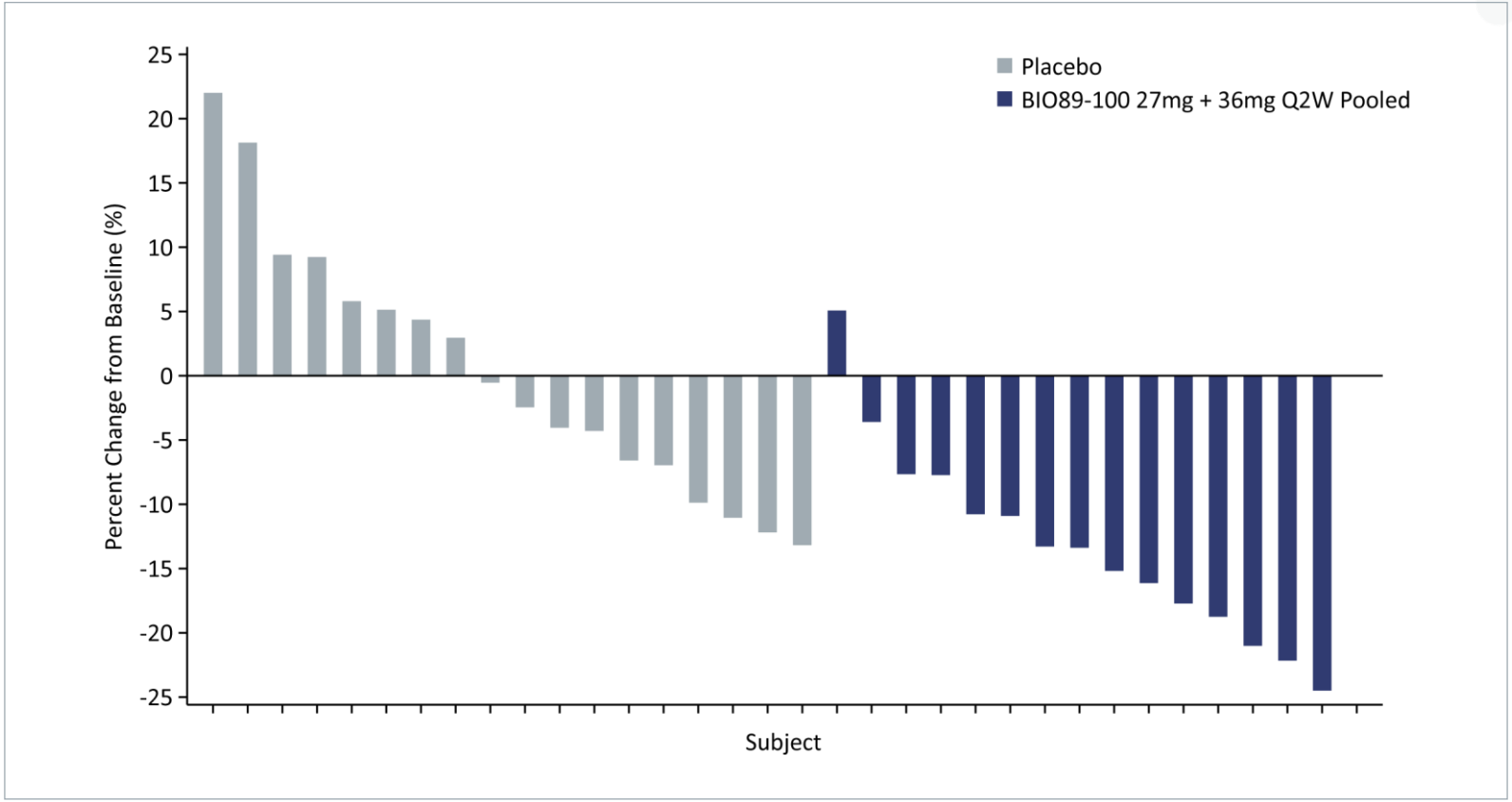
Significant Reduction in Spleen Volume With BIO89-100



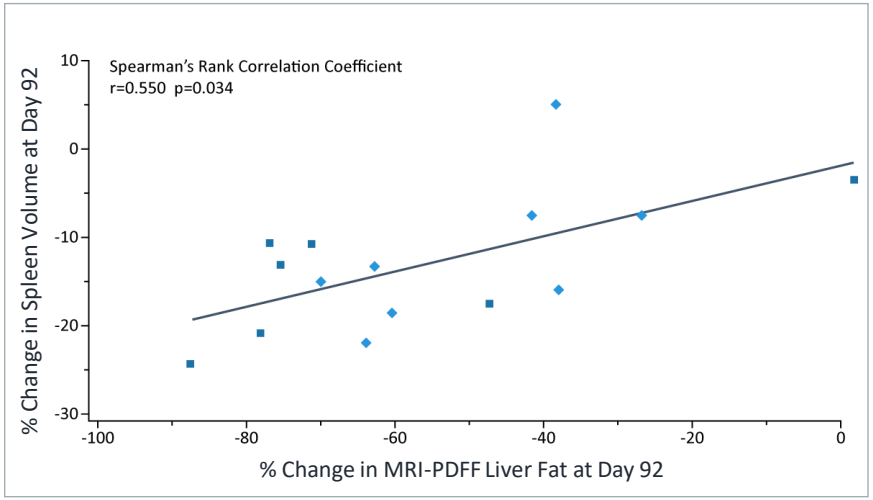
Percent changes from baseline to D50 and D92 were estimated using ANCOVA model adjusted for baseline SV.

Percent Spleen Volume Reduction (Individual Data) – Day 92



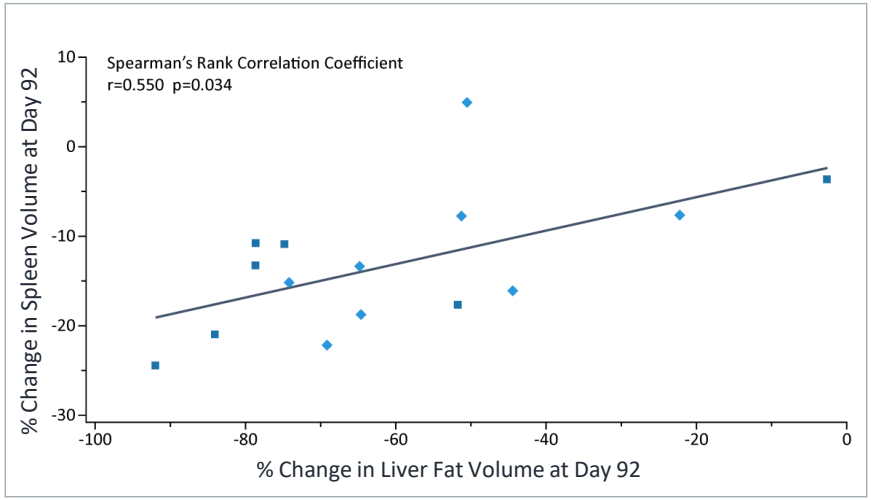
Spleen Volume Change Correlated to Change in Liver Fat at Day 92

% Change in MRI-PDFF



r = 0.55

% Change in Liver Fat Volume



r = 0.55

■ BIO89-100 27mg QW ◆ BIO89-100 36mg Q2W

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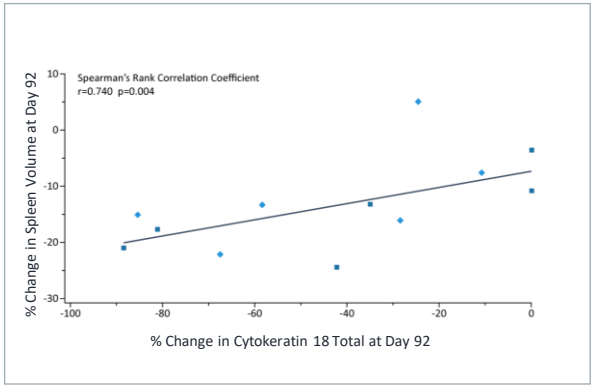
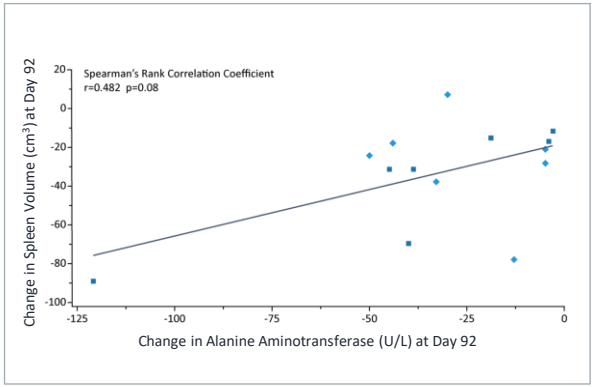
Spleen Volume Change Correlated With Change of CK-18 and ALT and Negatively Correlated with Platelet Count at Day 92

% Change CK-18



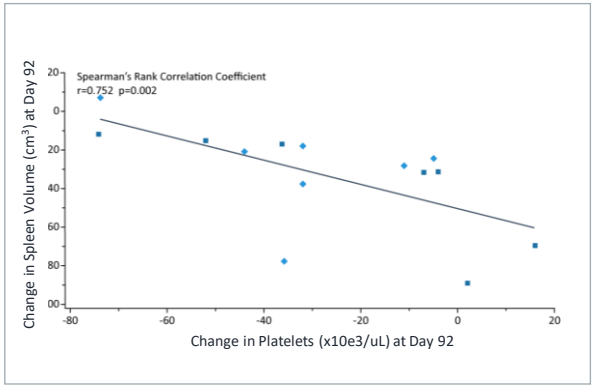
r = 0.74

ALT



r = 0.48

Platelet Count



r = 0.75

BIO89-100 27mg QW ◆ BIO89-100 36mg Q2W

Reduction in SV at day 92 appeared not to be correlated with change in VCTE score, ELF or Pro-C3 level

Post Hoc Analysis of NASH POC Study Demonstrated Meaningful Reduction in Spleen Volume that Correlated with other NASH Biomarkers

- SV at baseline was correlated with liver volume, VCTE score and BMI, and negatively correlated with platelet count
- Treatment with BIO89-100 led to a progressive, statistically significant decrease in SV compared to placebo (evident on Day 50, with further decrease on Day 92)
- SV reduction correlated with reductions in liver fat by MRI-PDFF, liver fat volume, CK-18 and ALT
- SV reduction was negatively correlated with platelet count
- Limitations include post-hoc analysis, small sample size, and lack of spleen stiffness evaluation

Conclusions:

- Progression in NAFLD is associated with subclinical increase in spleen volume and a parallel increase in liver stiffness and decrease in platelet count
- Reversal of NAFLD by normalization of liver fat and liver volume may be associated with improved portal flow thus decreasing spleen volume
- Further mechanistic studies are needed to confirm this hypothesis
- These data provide new insights regarding monitoring of SV in assessing treatment response in NASH clinical trials
- The role of SV measurement as a non-invasive tool for assessment of portal flow and the clinical significance of sub-clinical changes in spleen volume in subjects with NASH warrant further investigation