APPLICATION OF FIBROSCAN FOR HEPATIC SAFETY MONITORING IN EARLY CLINICAL STUDIES

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BACKGROUND

- Drug-induced liver injury (DILI) is a major clinical concern and regulatory challenge for investigational products. An estimated 50% of drugs in early clinical development with evidence of hepatoxicity are terminated before reaching the market [1].
- Intensive and growing research into diagnostic, predictive and prognostic biomarkers of DILI is underway [2], and imaging biomarkers may also serve as a valuable DILI risk-mitigation tool.
- FibroScan® is a non-invasive, ultrasound-like device used to measure hepatic fibrosis as a function of liver stiffness. The results are intended to be interpreted in conjunction with FIB4 values, a composite serum fibrosis biomarker based on AST, ALT, and platelet count. FIB4 positively correlates with liver fibrosis stage in several disease conditions.
- FibroScan has been used extensively in nonalcoholic steatohepatitis (NASH) and Hepatitis B and C indications clinical studies. In addition, this non-invasive tool has been applied for DILI monitoring of the potential effect of methotrexate-induced hepatic fibrosis in psoriasis, arthritis and Crohn's patients [3, 4].
- Cerecin, a biopharmaceutical company developing novel treatments for neurological conditions, is interested in understanding the DILI liability of their drug product, AC-SD-03, a formulation of tricaprilin.

METHODS

- Twelve healthy, older (>50 years) male and female participants with a BMI of 18-32 kg/m^2 participated in a multiple-dose, open-label titration clinical trial (NCT 04268953).
- Doses of AC-SD-03 were gradually titrated from 12.5g (containing 5 g tricaprilin) to 75g (containing 30g tricaprilin) BID, over 24 days.
- Liver stiffness assessments were performed using FibroScan 502 Touch (Echosens, Paris), measured as Velocity Controlled Transient Elastography (VCTE), by certified nurse operators on Day -1 (baseline) and Day 24.
- Results were analyzed by paired t-test. Variability was examined as coefficient of variance (CV%) and by Bland-Altman analysis.

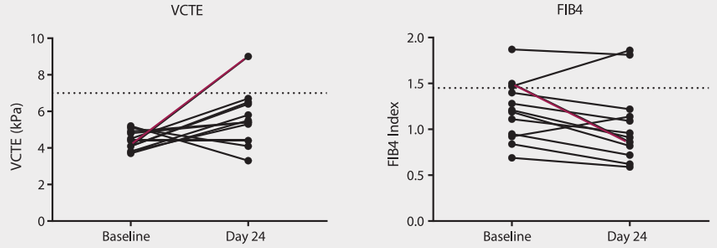
TABLES & FIGURES

TABLE 1. SUMMARY OF BASELINE CHARACTERISTICS

Demographic Characteristic	Study Population (n=12)
Age (years)	60.3±4.45 (54 – 69)
Gender (Male/Female)	5 M / 7 F
Weight (kg)	78.1±11.9 (57.8 – 97.9)
BMI (kg/m^2)	27.5±3.0 (20.3 – 30.7)
AST (IU/L)	21.5±4.6 (15 – 31)
ALT (IU/L)	19.8±6.6 (13 – 36)
PLT (thou/uL)	260.8±65.1 (172 – 415)

Data presented as mean±SD with range in parenthesis.

FIGURE 1. DIVERGENT VCTE AND FIB4 VALUES



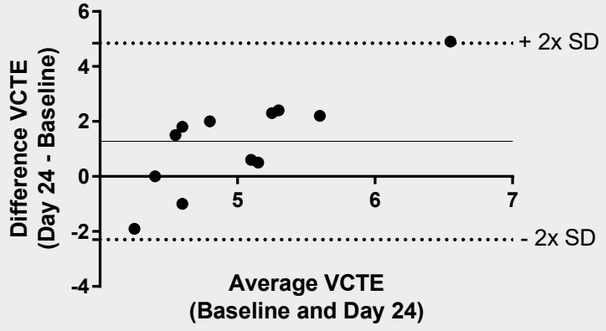
Dotted line represents literature-based cut-offs for VCTE >7kPa and FIB4 >1.3, which are indicative of liver fibrosis. Outlier subject highlighted in pink.

TABLE 2. VCTE AND SERUM SCORES

Parameter	Baseline	Day 24	CV%	p-value
VCTE (kPa)	4.4±0.5 (3.7 – 5.2)	5.7±1.4 (3.3 – 9.0)	18% (0 – 53%)	0.03
FIB4 Index	1.20±0.33 (0.69 – 1.87)	1.05±0.41 (0.59 – 1.86)	10% (2 – 38%)	0.07
AST/ALT	1.15±0.27 (0.74 – 1.67)	1.09±0.43 (0.43 – 1.91)	14% (3 – 42%)	0.45

Data presented as mean±SD with range in parenthesis.
Previous assessments found intra-subject CV% ranged between 13-42%.

FIGURE 2. BLAND-ALTMAN ANALYSIS



RESULTS

- All scans were successful as determined by an interquartile range (IQR) <30%.
- All but 3 participants demonstrated in increase in VCTE at Day 24.
- Average VCTE increased by 29% at the end of study, though deemed not a clinically significant increase. Meanwhile, FIB4 and AST/ALT ratio slightly decreased by 13% and 7% by Day 24, respectively.
- The high variation was mainly attributed to one participant who had a VCTE score >7 kPa at the end of the study. Interestingly, this participant displayed divergent FIB4 results, as their FIB4 value dropped by nearly half from 1.50 to 0.86.
- There were no clinical symptoms associated with the increase in VCTE and no change in liver function tests.
- Bland-Altman analysis, which assesses the agreement between two quantitative methods of measurement, revealed all but the one outlier participant fell within 2x SD.

DISCUSSION & CONCLUSIONS

- To our knowledge, this is the first study to incorporate FibroScan as a liver safety assessment in early clinical drug development.
- The majority of participants demonstrated an increase in VCTE coupled with reduced FIB4 values after dosing, resulting in an inconclusive response on liver stiffness.
- Despite divergent VCTE and FIB4 results, no clinically significant findings were observed in liver stiffness after 24 days of investigation.
- Factors that can influence intra-subject variability include operator experience, fasting conditions and probe size. Controlling for these factors may help minimize variability.
- Excluding this one participant from the analysis, the upper limit of CV% was reduced to 32%, and in line with previous results as well as data from published studies [5, 6].
- Overall, FibroScan is a non-invasive tool to detect hepatic manifestations and can play an important role in drug safety monitoring, though further validation is required for this application.

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