SimulationsPlus

MIDD+22

Model Informed Drug Development

Yo-Yo Dieting Predicted to Contribute to Fibrosis Score Reductions in Untreated (Placebo) Cohorts

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Please note: this presentation, including questions from the audience, is being recorded and may be made available.

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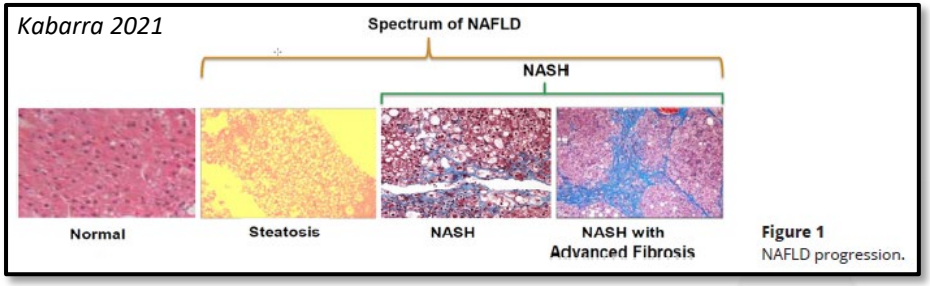
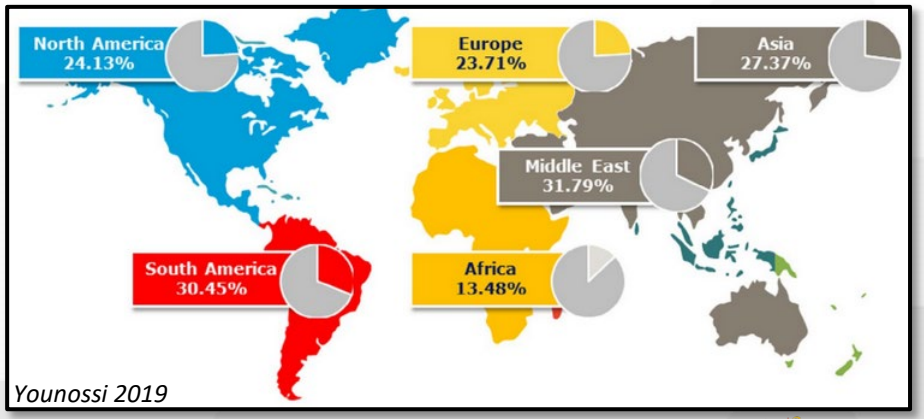
Non-alcoholic Fatty Liver Disease (NAFLD) / Non-alcoholic Steatohepatitis (NASH)

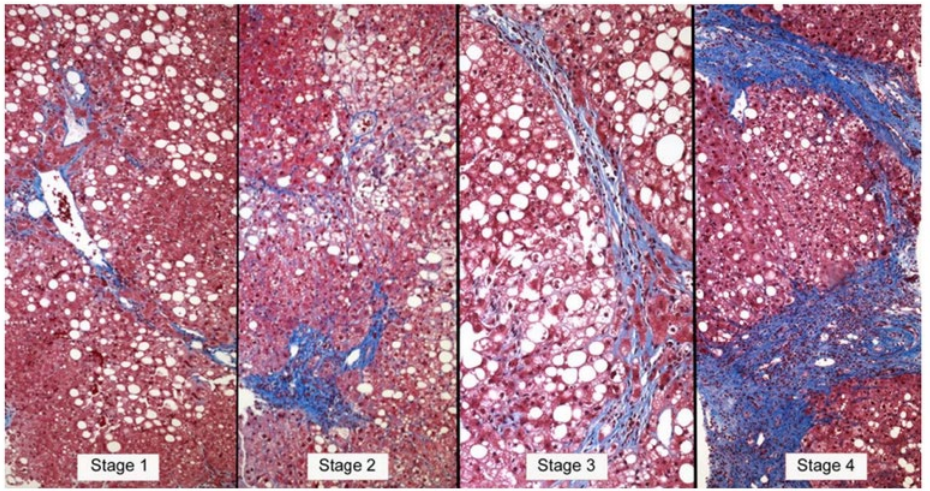
- NAFLD/NASH represents a spectrum of chronic liver disease
- Global prevalence is estimated at ~25% in the adult population with no approved drug treatment
  - Substantial opportunity to improve health for many patients by developing treatments





Histopathological Endpoints in NAFLD/NASH

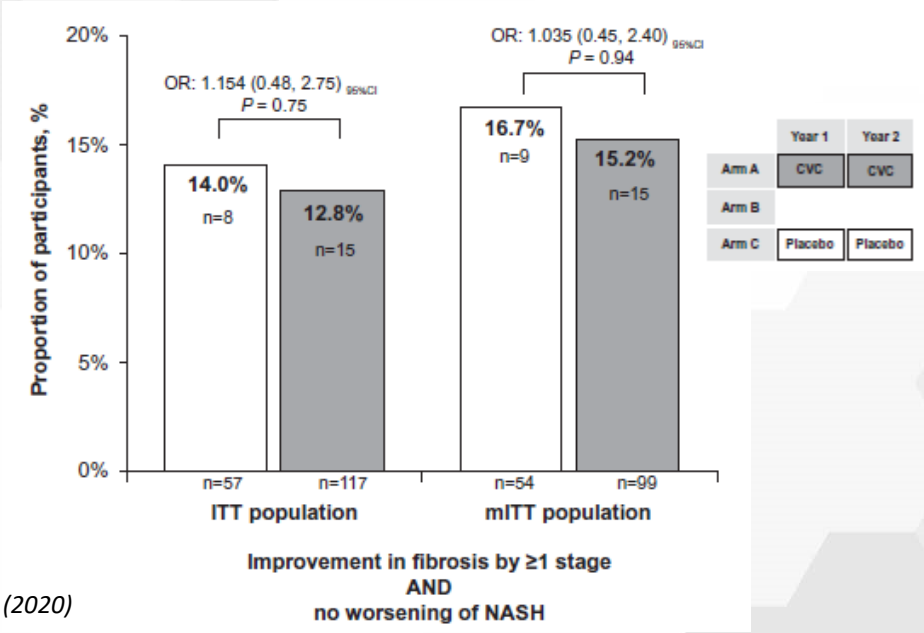
- Liver biopsy is the definitive technique for diagnosis and classification of NAFLD
- NAFLD Activity Score (NAS), a summary score ranging from 0-8, developed to grade key features of steatosis, hepatocellular ballooning, and lobular inflammation
- Fibrosis, representing disease stage, scored separately



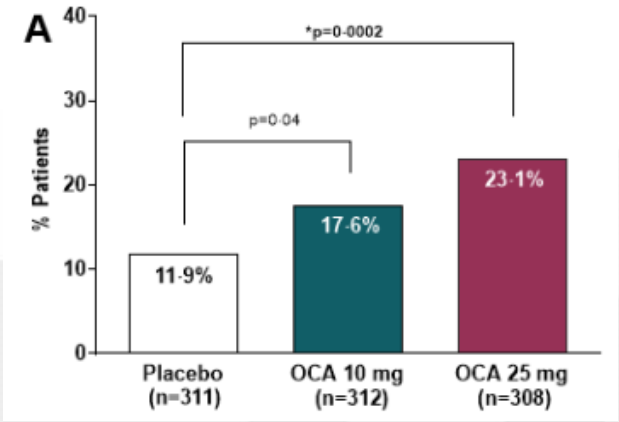
Younossi 2018

In Clinical Trials, 10-20% of Placebo-Treated Patients Demonstrate Fibrosis Improvement

- Randomized, placebo-controlled clinical trials with biopsy proven NASH/NAFLD, in which biopsies were collected to evaluate clinical endpoints



Ratziu (2020)



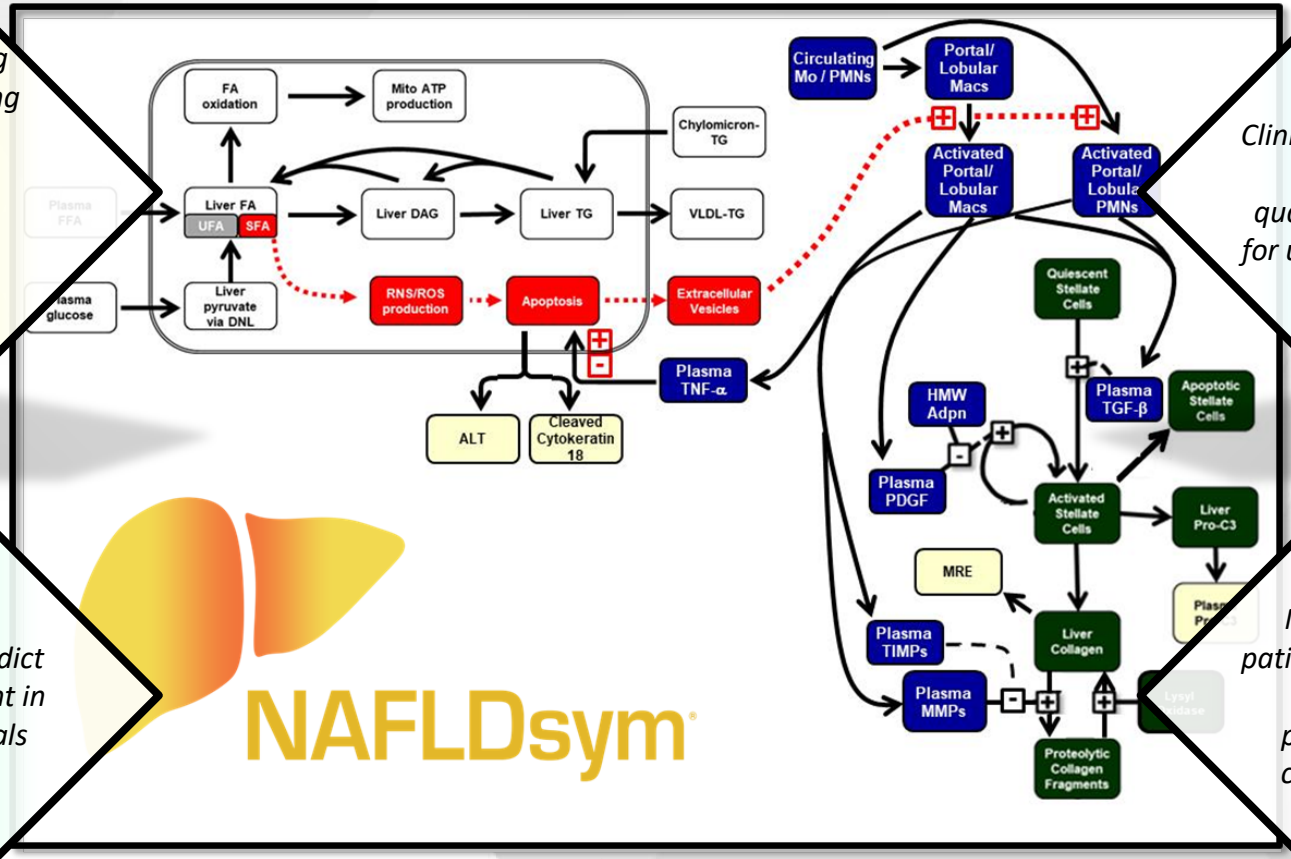
Younossi (2019)

What might account for fibrosis improvement in the placebo-treated groups?

NAFLDsym, a QSP Model of NAFLD, is Uniquely Positioned to Address this Question

Multiple interacting sub-models, including

- *Steatosis*
- *Lipotoxicity*
- *Inflammation*
- *Fibrosis*
- *Biomarkers*
- *Weight gain/loss*

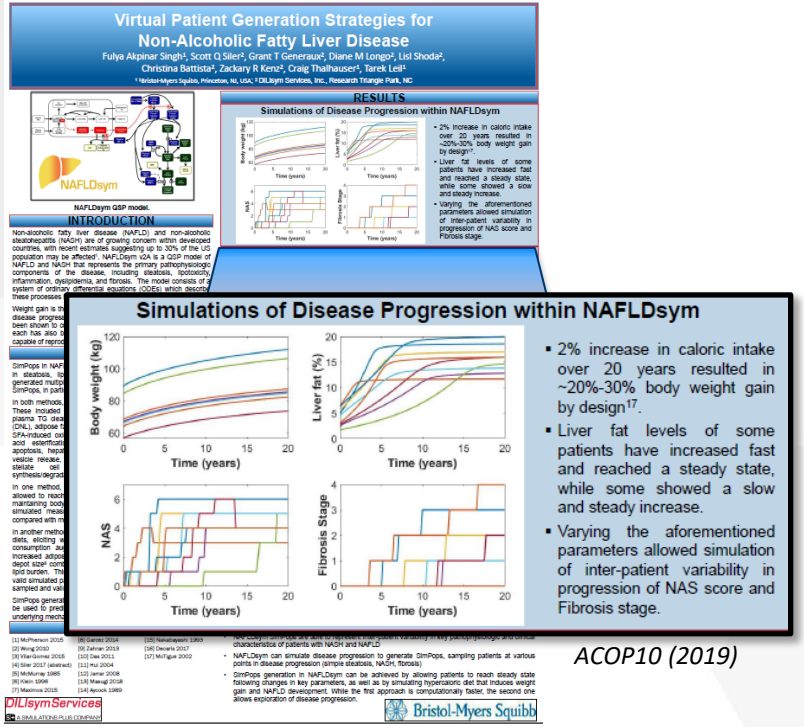


Clinical data from literature used to establish quantitative relationships for underlying biochemistry

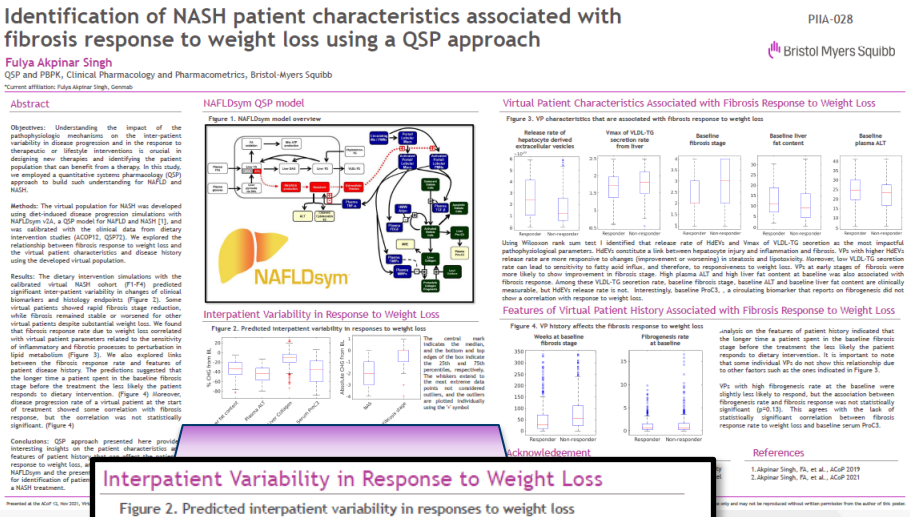
Provides ability to predict responses to treatment in simulated clinical trials

Numerous simulated patients (SimPops) included to account for pathophysiologic and clinical heterogeneity

NAFLDsym Previously Applied to Explore Disease Progression and Weight Loss



ACOP10 (2019)

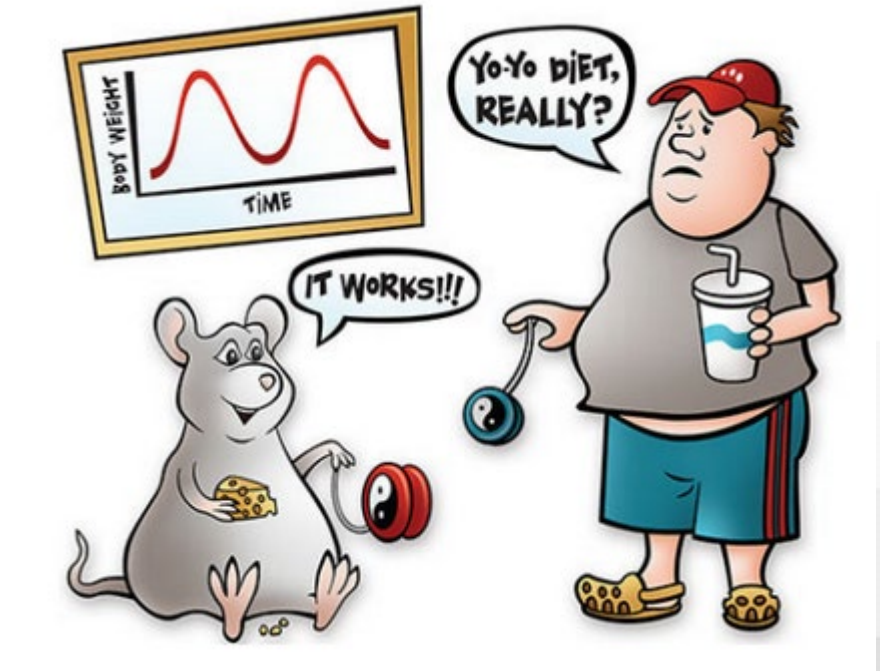


ACOP12 (2021)

What if patient behavior (particularly diet) in the placebo group is influenced by being in the clinical trial?

Periodic Weight Cycling in Response to Changing Diet/Activity is Known as Yo-Yo Dieting

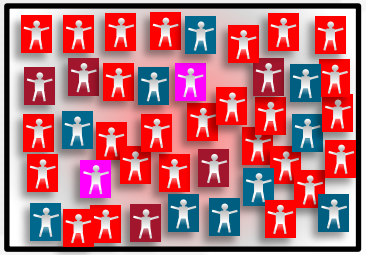
- Intentional weight loss followed by unintentional weight regain is a relatively common occurrence
- Although this weight cycling has been associated with morbid health conditions and increasing mortality, recent analyses and data argue against purely adverse effects (Smith 2018, Mehta 2014)
- **Hypothesis**: In a clinical trial, unintentional weight loss may occur in anticipation of upcoming regular clinic visits, followed by unintentional weight gain after the visit



Di Garmanio (2018)

Simulated Yo-Yo Dieting in Otherwise Untreated SimCohorts

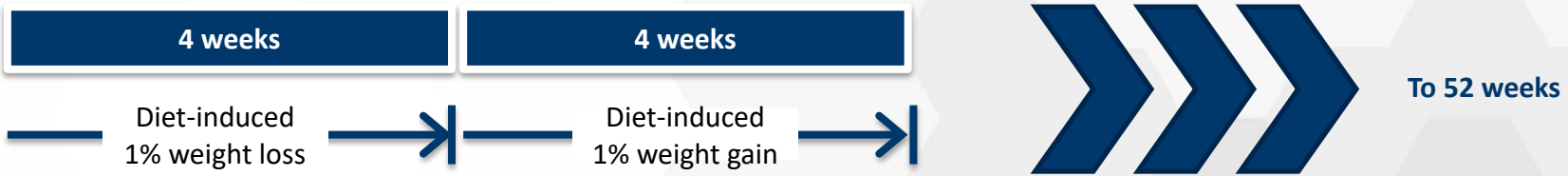
SimCohorts represent inter-patient variability



Baseline characteristics of N=90 SimCohorts

Body weight (kg)	Liver fat (%)	Plasma ALT (U/L)	NAS (score)	F2 Fibrosis (%)	F3 Fibrosis (%)
89.1 ± 19.4	17 ± 5	50 ± 12	5.6 ± 3.2	35/90 (39)	55/90 (61)

Simulation plan:



Simulations Predict Yo-Yo Dieting Can Reduce Fibrosis Scores Similar to Clinical Reports

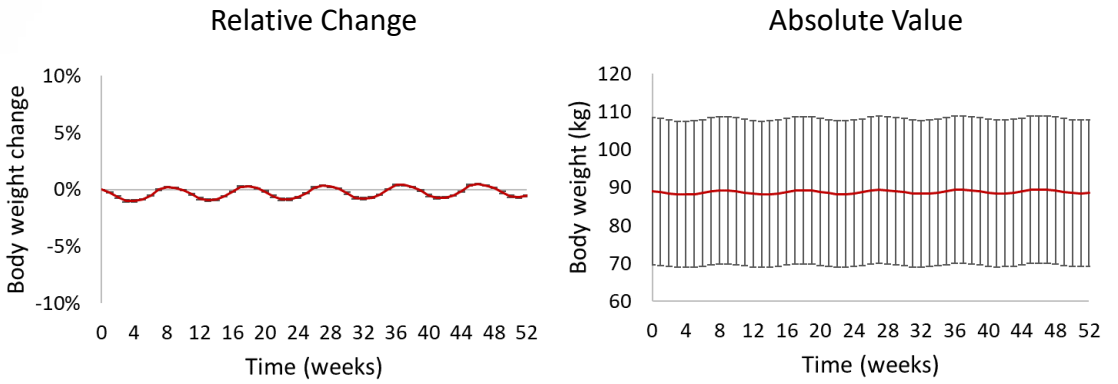
- Successive cycles of mild (1%) weight loss and weight gain are predicted to persistently reduce fibrosis scores in ~10% of subjects
- By contrast, the NAFLD activity score (NAS) reflecting histologic measures of steatosis, lobular inflammation, and ballooning, is predicted to be largely unchanged

Predicted Histologic Reductions

Time (weeks)	Fibrosis reduction ≥1 stage (%)	NAS reduction ≥2 points (%)
13	6	4
26	10	0
39	12	0
52	10	0

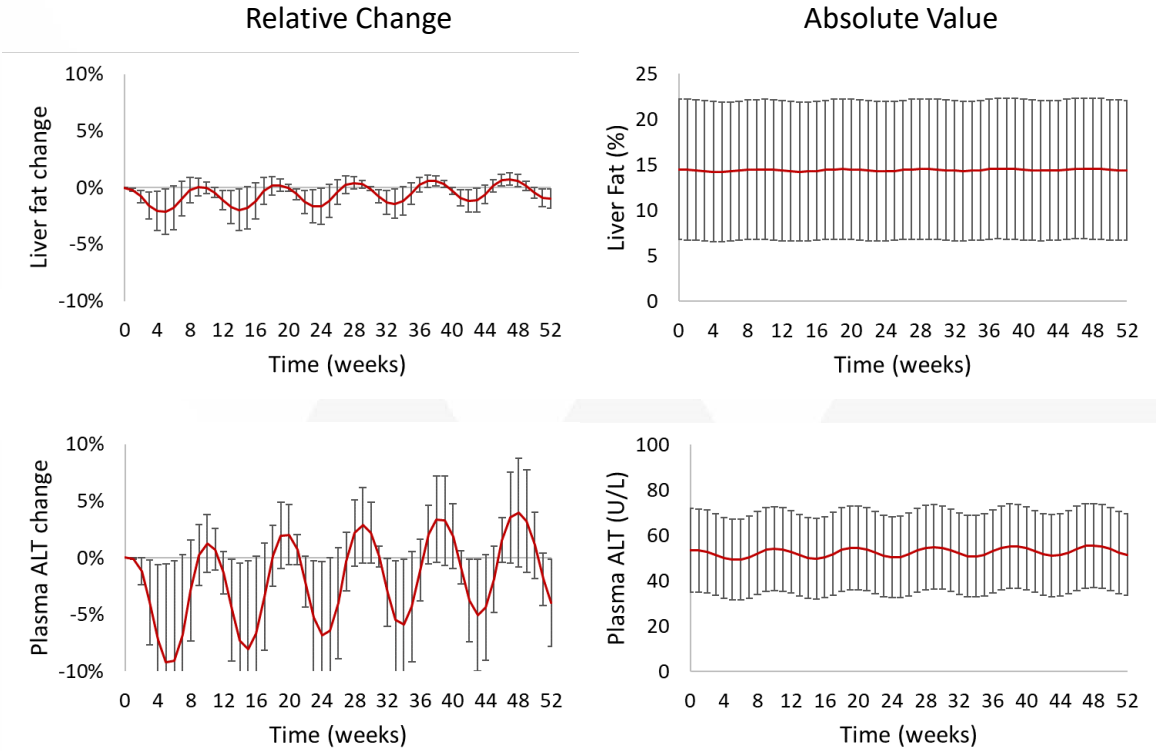
Predicted Dynamic Changes in Body Weight Confirm Yo-Yo Dieting in SimCohorts

- Mean body weight oscillates by ~1% every 4 weeks by design
- Absolute body weight measurements demonstrate mild oscillations that would likely be clinically undetectable



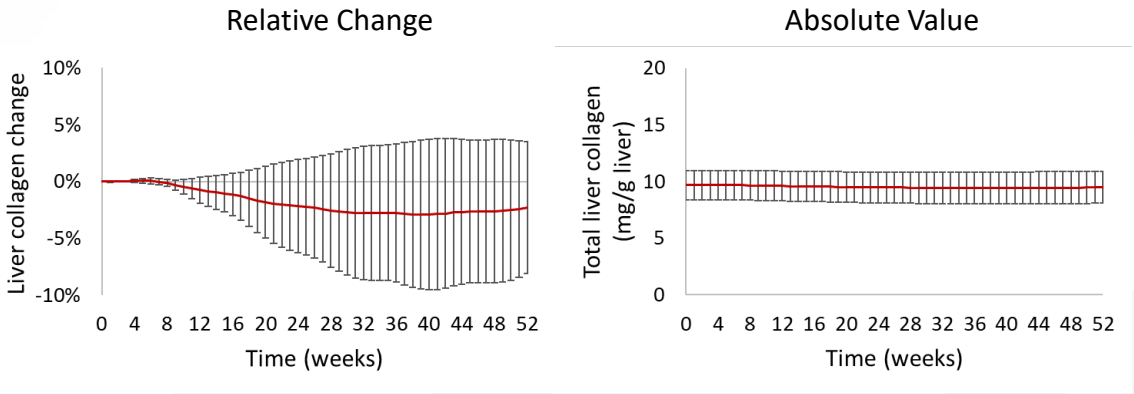
Predicted Changes in Liver Fat and ALT Illustrate Dynamic Changes That Mirror Weight Change

- Liver fat and ALT oscillate on similar time scales as diet
- Absolute changes are relatively minor but might be detected depending on timing of measurement



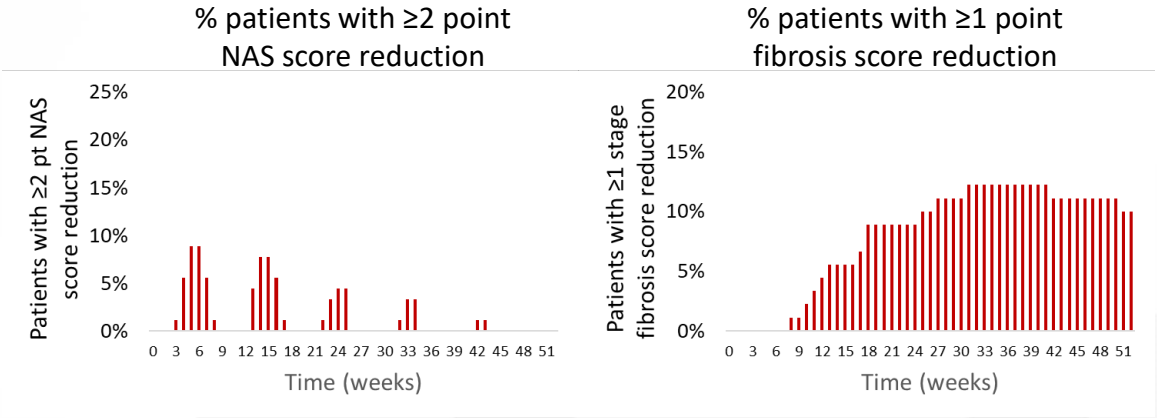
Predicted Changes in Liver Collagen Illustrate Different Dynamics for Fibrotic Response

- Changes in fibrosis reflect slower dynamics than those related to steatosis or lipotoxicity
- Absolute changes are modest
- Fibrosis scores reflect amount and location of collagen in the hepatic acinus



Clinical Endpoints are Differentially Affected by Fast vs. Slow Dynamics

- Measurement timing more likely affects endpoints governed by fast dynamics



Conclusions

- Yo-yo dieting could contribute to relatively high placebo cohort fibrosis response rates in NASH clinical trials
- Reductions in fibrosis score are due to the slow rate of change of collagen relative to steatosis and lipotoxicity
- Change in fibrosis manifests over time with continued yo-yo dieting
- Depending on timing of measurement, changes in liver fat and plasma ALT may be detectable in patients undergoing yo-yo dieting

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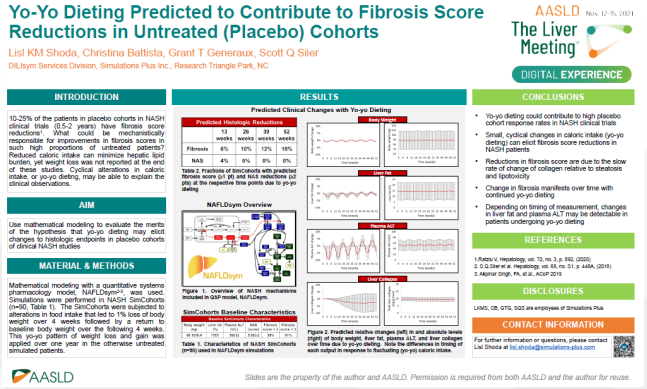

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Q&A

Questions & Answers