# The NEXT GENERATION HepQuant Tests Measure Reduction in Risk for Clinical Events in Compensated NASH Cirrhosis Subjects Treated with Resmetirom

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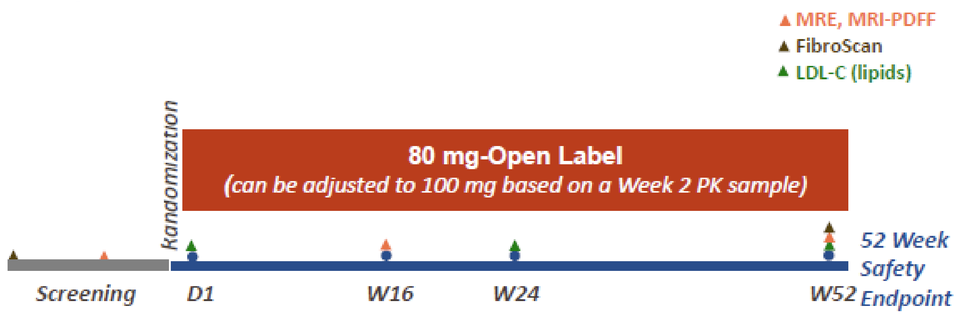
## BACKGROUND

- The HepQuant SHUNT test quantifies liver function and physiology.
- Simplified versions (V2.0 and DuO) require fewer blood samples and shorter testing time.
- MAESTRO-NAFLD-1 (NCT04197479) was a 52-week Phase 3 trial to evaluate the safety and tolerability of resmetirom, a thyroid hormone receptor-β agonist being studied for the treatment of NASH.[1]
  - MAESTRO-NAFLD-1 included an open-label active resmetirom treatment arm in patients with well-compensated (Child-Pugh A [CP-A]) NASH cirrhosis (**Figure 1**).

### Figure 1. MAESTRO-NAFLD-1: Open-label Arm in Patients with Well-compensated NASH Cirrhosis




## OBJECTIVE

- To determine whether next generation HepQuant tests could detect treatment effects in MAESTRO-NAFLD-1 (NCT04197479)

## METHODS

- 34 subjects with compensated NASH cirrhosis underwent baseline testing and subsequent retesting at 28 and 48 weeks.
- Eligibility: at least 3 metabolic risk factors and NASH cirrhosis diagnosed by liver biopsy or accepted criteria
- SHUNT test
  - Intravenous 13C-CA and oral d4-CA were administered
  - Blood sampled at 0, 5, 20, 45, 60, and 90 minutes for serum cholate concentrations
- AUCs were calculated by a compartmental model (McRae et al., 2023)[2]:
  - SHUNT V2.0: IV and oral data at 20 and 60 minutes
  - DuO: only oral data at 20 and 60 minutes
- Risk ACE was calculated for each subject from the baseline and weeks 28 and 48 disease severity index (DSI)

## RISK ACE

- A Poisson model (Risk ACE) estimated the annual clinical event rate based on 220 subjects with 52 clinical events from the HALT-C Trial.
- The result is an event rate (clinical events per person-year).
- Model A: Relationship with baseline DSI (denoted by $dsi_0$):

$$Y = \beta_0 + \beta_1 dsi_0$$

- Model D: Relationship with baseline DSI and change in DSI (denoted $dsi_\Delta$)

$$Y = \beta_0 + \beta_1 dsi_0 + \beta_2 dsi_\Delta$$

- Difference from baseline is represented by the difference of Risk ACE Model A and Model D (**Table 1**)

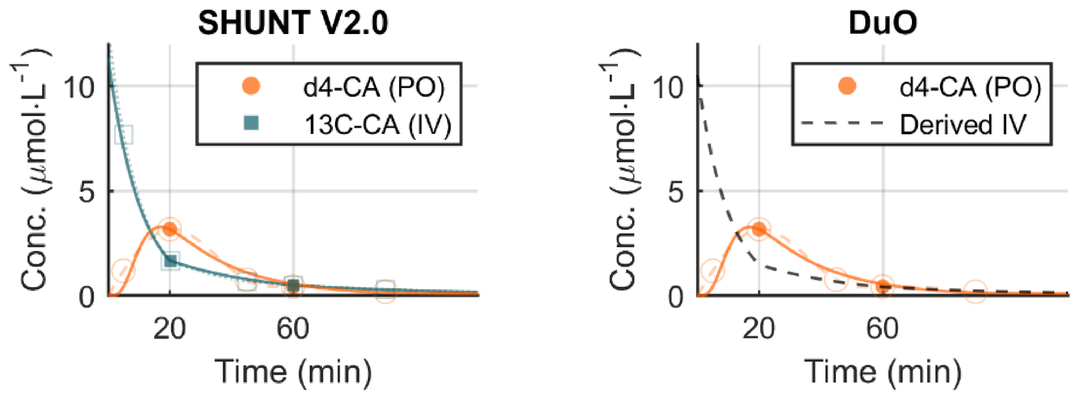
### Table 1. Difference of Risk ACE Model A and Model D

| | Coefficient Value |
|---|---|
| Model A | |
| $\beta_0$ | -6.300 |
| $\beta_1$ | 0.150 |
| Model D | |
| $\beta_0$ | -7.201 |
| $\beta_1$ | 0.173 |
| $\beta_2$ | 0.139 |

## RESULTS

- HepQuant test versions DuO and SHUNT V2.0 significantly simplify test administration, reducing blood samples by two-thirds and test time by one-third (**Figure 2**).

### Figure 2. Reduction of Blood Sampling and Test Time by HepQuant Tests

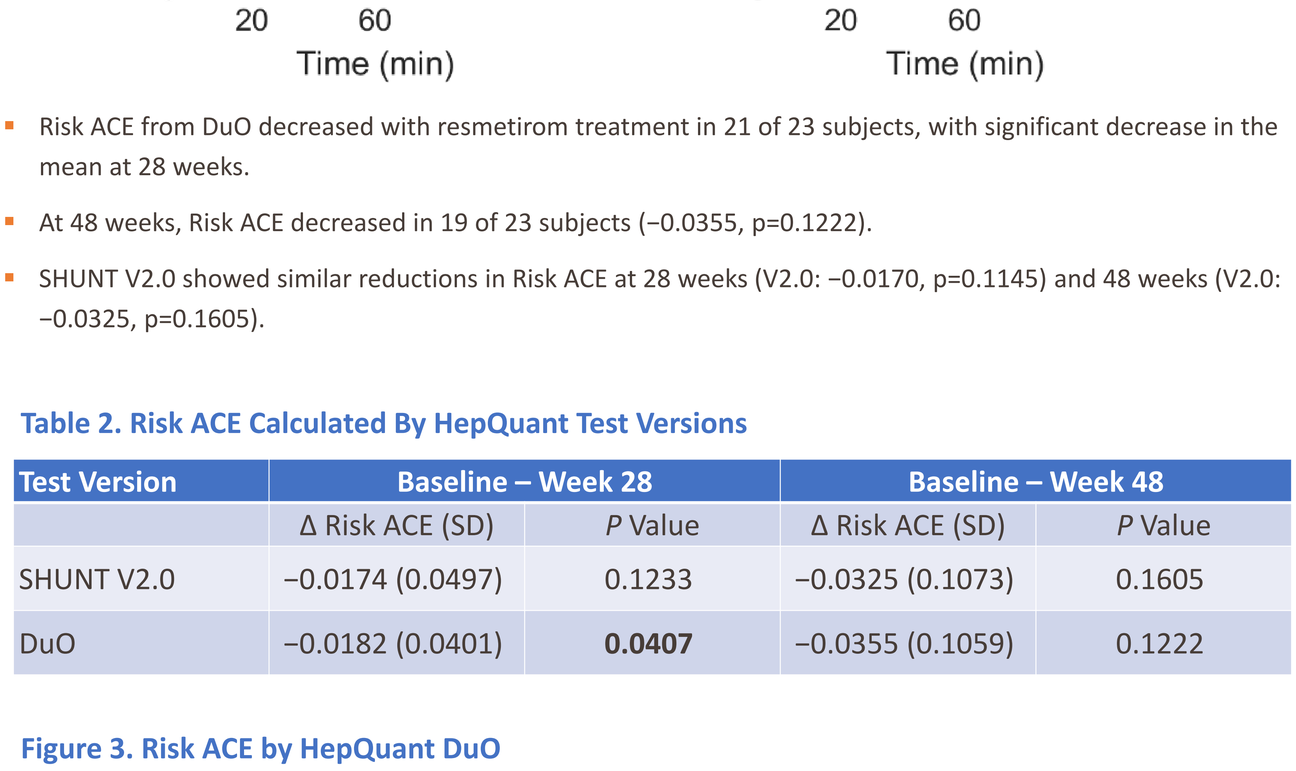



- Risk ACE from DuO decreased with resmetirom treatment in 21 of 23 subjects, with significant decrease in the mean at 28 weeks.
- At 48 weeks, Risk ACE decreased in 19 of 23 subjects (−0.0355, p=0.1222).
- SHUNT V2.0 showed similar reductions in Risk ACE at 28 weeks (V2.0: −0.0170, p=0.1145) and 48 weeks (V2.0: −0.0325, p=0.1605).

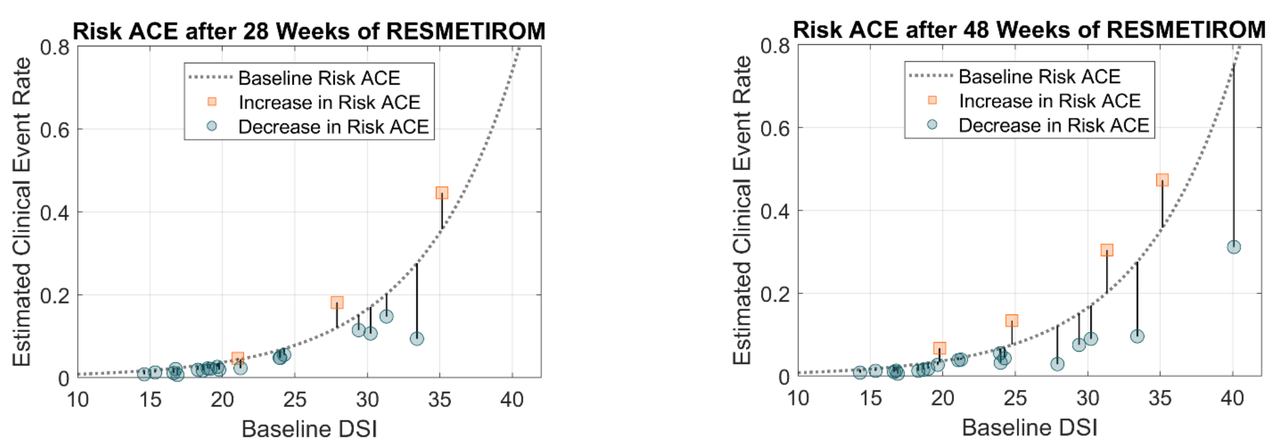
### Table 2. Risk ACE Calculated By HepQuant Test Versions

| Test Version | Baseline – Week 28 | | Baseline – Week 48 | |
|---|---|---|---|---|
| | Δ Risk ACE (SD) | *P* Value | Δ Risk ACE (SD) | *P* Value |
| SHUNT V2.0 | −0.0174 (0.0497) | 0.1233 | −0.0325 (0.1073) | 0.1605 |
| DuO | −0.0182 (0.0401) | **0.0407** | −0.0355 (0.1059) | 0.1222 |

### Figure 3. Risk ACE by HepQuant DuO




### Figure 4. Risk ACE by HepQuant SHUNT V2.0




## CONCLUSIONS

- **Next generation HepQuant tests measured a reduction in estimated clinical event rate after 28 weeks of resmetirom.**
- **HepQuant DuO provides a sensitive and interpretable metric of risk for All Clinical Events in monitoring patients.**
- **DuO and SHUNT V2.0 are easier to administer and less invasive, thus, having the potential to be more widely accepted by care providers administering the test and by patients receiving the test.**
- **Further evaluation and clinical validation of DuO and Risk ACE is warranted.**

## REFERENCES

1. Harrison et al., Lancet 2019, 394:2012-24
2. McRae et al., Transl. Res. 2023, 252:53-63

## CONFLICTS OF INTEREST

MPM is a paid consultant for HepQuant LLC. SMH and GTE are employees and equity members of HepQuant LLC. RT is an employee of Madrigal Pharmaceuticals. MPM, SMH, and GTE have provisional patents pending.