Poster #8

MONARCH A PHASE 2B, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF MIRICORILANT IN ADULT PATIENTS WITH NONALCOHOLIC STEATOHEPATITIS/METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (NASH/MASH)

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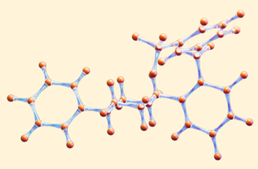
Background

- Cortisol, a hormone that regulates metabolism and stress, has been implicated in the development and progression of NAFLD (also known as MASLD)[1,2]
  - Cortisol is a natural steroid ligand for the GR
  - Binding of cortisol to the GR increases availability of energy substrates, such as FFAs, for response to stress and daytime activities
  - Cortisol can contribute to excess FFAs in the liver by increasing FFA uptake and de novo lipogenesis

Miricorilant (CORT118335)

- An orally administered, nonsteroidal SGRM that acts as a mixed agonist/antagonist of the GR and a modest antagonist of the MR[3]
  - Has high affinity for the GR (6-fold affinity for GR vs MR)
- May reduce hepatic steatosis by modulating cortisol activity in the liver
- Reversed and prevented hepatic steatosis by preventing lipid accumulation in the liver, and showed reductions in inflammation, fibrosis stage, and NAS in preclinical models of NAFLD/NASH (also known as MASH)[4]



Phase 1b, multi-cohort, open-label, dose-finding trial (NCT05117489)[5,6]

- Adult patients with presumed NASH/MASH were treated with miricorilant doses 30–200 mg daily or intermittently for 12 or 24 weeks
- Miricorilant 100 mg twice weekly had the best benefit-risk profile at week 12
  - This dosing schedule provided a gradual reduction in liver fat over 12 weeks without an associated rise in hepatic transaminase levels
    - Mean relative reduction in LFC of −28.2% (SD: 13.5)
    - Decline in liver enzymes, with a mean change from baseline of −4.0 (SD: 21.4) for ALT and −6.0 (SD: 7.2) for AST
- Additionally, this dose was safe, well-tolerated, and resulted in improved hepatic, lipid, and glycemic markers

⇨ Based on these findings, the phase 2b MONARCH study was initiated to further evaluate the safety and efficacy of miricorilant 100 mg twice weekly in patients with biopsy-confirmed NASH/MASH

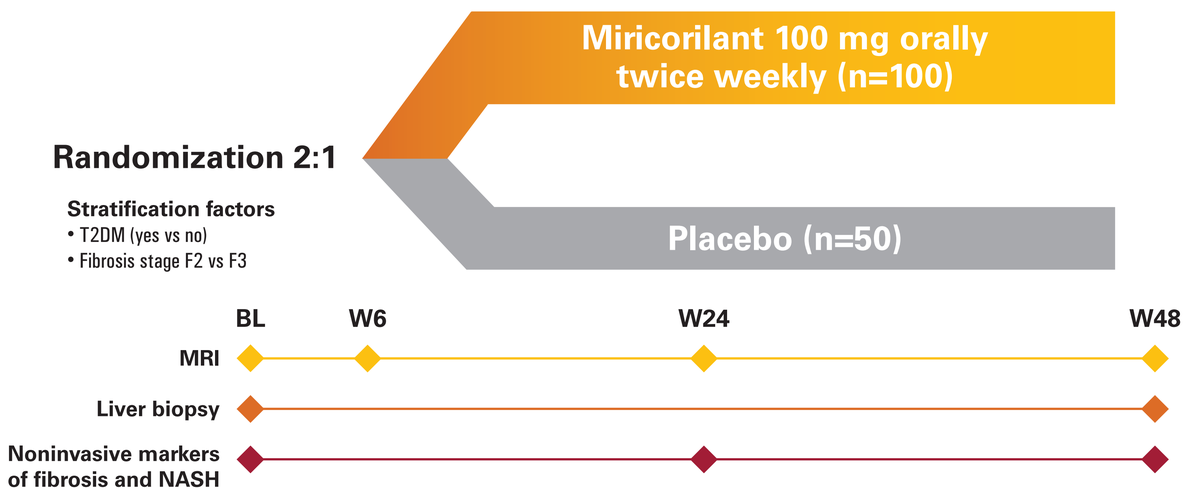
ALT, alanine aminotransferase; AST, aspartate aminotransferase; FFA, free fatty acid; GR, glucocorticoid receptor; LFC, liver fat content; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MR, mineralocorticoid receptor; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; SD, standard deviation; SGRM, selective glucocorticoid receptor modulator.

Summary & Conclusions

- There remains an unmet need for effective NASH/MASH treatments, as there are currently no FDA-approved therapies
- Miricorilant, an oral, nonsteroidal selective glucocorticoid receptor modulator (SGRM), may offer a promising new strategy for the treatment of NASH/MASH
- Previous clinical trials have shown that twice-weekly miricorilant 100 mg was safe, well tolerated, and resulted in reduced LFC and improved hepatic, lipid, and glycemic markers[5]
- MONARCH is a phase 2b, double-blind, placebo-controlled, randomized study evaluating efficacy and safety of miricorilant in patients with biopsy-confirmed noncirrhotic NASH/MASH
- MONARCH is actively enrolling at sites across the United States

FDA, U.S. Food and Drug Administration.

MONARCH Study Design



- MONARCH (NCT06108219) is a phase 2b, double-blind, placebo-controlled, randomized study evaluating miricorilant in patients with biopsy-confirmed noncirrhotic NASH/MASH
- Approximately 150 adults are being randomized 2:1 to miricorilant 100 mg or placebo twice weekly for 48 weeks

Endpoints

- **Primary endpoint:** Change from baseline in LFC at week 24, assessed by MRI-PDFF
- **Key secondary endpoint:** Resolution of steatohepatitis and no worsening of liver fibrosis at week 48, assessed by biopsy
- **Other secondary and exploratory endpoints:** Changes in liver enzymes, liver fibrosis markers (including ELF score and TGF-beta), inflammatory markers, glycemic markers, and lipids, as well as safety and pharmacokinetics

BL, baseline; ELF, enhanced liver fibrosis; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; T2DM, type 2 diabetes mellitus; TGF-beta, transforming growth factor beta; W, week.
Site map as of 12/11/2023. Additional sites to be opened.

Key Inclusion and Exclusion Criteria

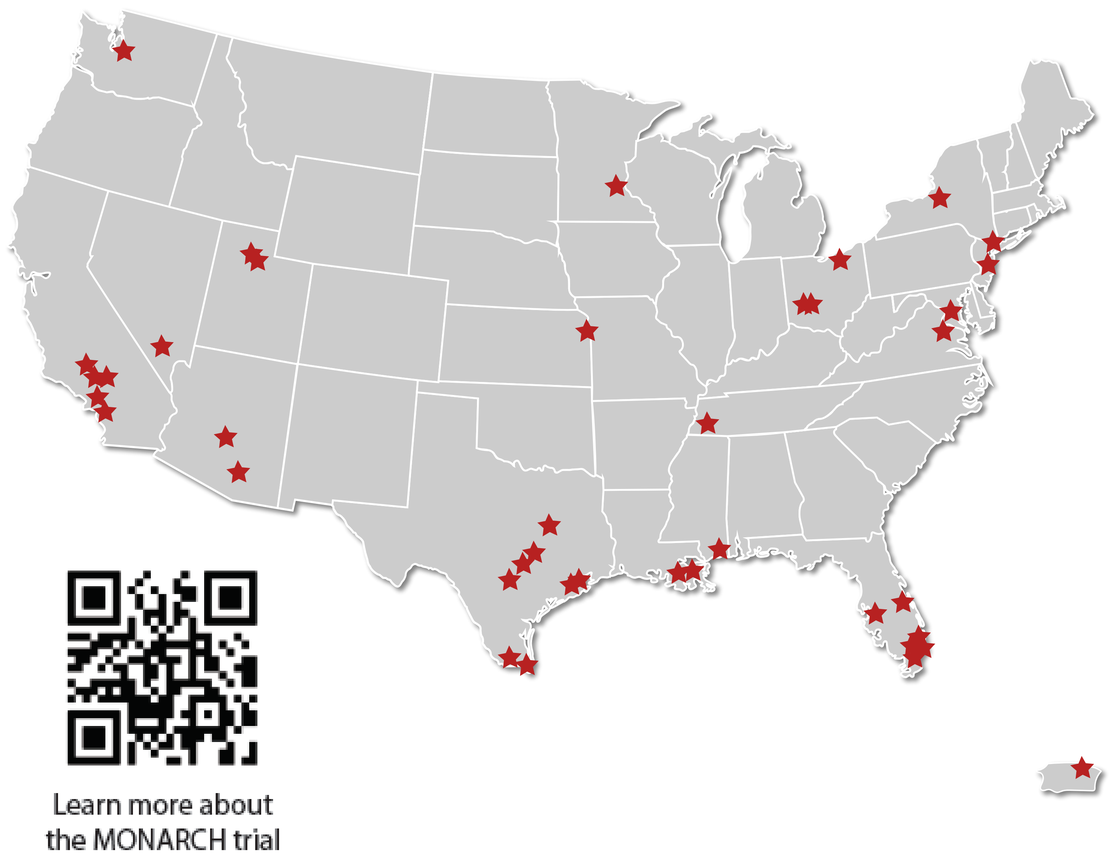
Inclusion	Exclusion
• 18–75 years old	
• Stable body weight	• BMI <18 kg/m^2 or >45 kg/m^2 • Successful weight loss surgery within 2 years • >5% weight change within 3 months of screening
• MRI-PDFF with ≥8% steatosis within 6 weeks of baseline • FibroScan® liver stiffness measurement ≥8 kPa	• Significant alcohol consumption • Use of drugs associated with NAFLD/MASLD, resmetirom, pioglitazone, high-dose vitamin E, GLP-1 agonists

• Histological diagnosis of NASH/MASH
  ○ NAS ≥4
  ○ NASH-CRN fibrosis score 2 or 3
	• Any other chronic liver disease
	• Cirrhosis
	• Hepatic decompensation

• AST >17 U/L (women) and >20 U/L (men)	• Abnormal screening laboratories:
	  ○ AST >5× ULN
	  ○ ALT >5× ULN
	  ○ eGFR <60 mL/min/1.73 m^2
	  ○ Creatine kinase >3× ULN

• Risk factors for NASH:
  ○ Type 2 diabetes OR
  ○ Metabolic syndrome, based on ≥3 of the following:
  ○ Fasting blood glucose ≥100 mg/dL
  ○ Systolic blood pressure ≥130 mmHg or diastolic ≥85 mmHg
  ○ Serum triglycerides ≥150 mg/dL
  ○ Serum HDL <40 mg/dL (men) or <50 mg/dL (women)
  ○ Overweight or obese
	• Type 1 diabetes

BMI, body mass index; GLP-1, Glucagon-like peptide-1; HDL, high-density lipoprotein; NASH-CRN, NASH Clinical Research Network; ULN, upper limit of normal.



Learn more about the MONARCH trial

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Presenter Disclosures

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