Poster # MASHTAG.2025.A11

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

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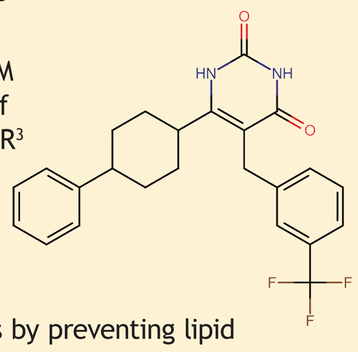
Background

- Cortisol, a hormone that regulates metabolism and stress, has been implicated in the development and progression of 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 FFA uptake 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 higher 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 MASLD/MASH[4]



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

- Adult patients with presumed 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 twice-weekly miricorilant in patients with biopsy-confirmed or presumed non-cirrhotic MASH

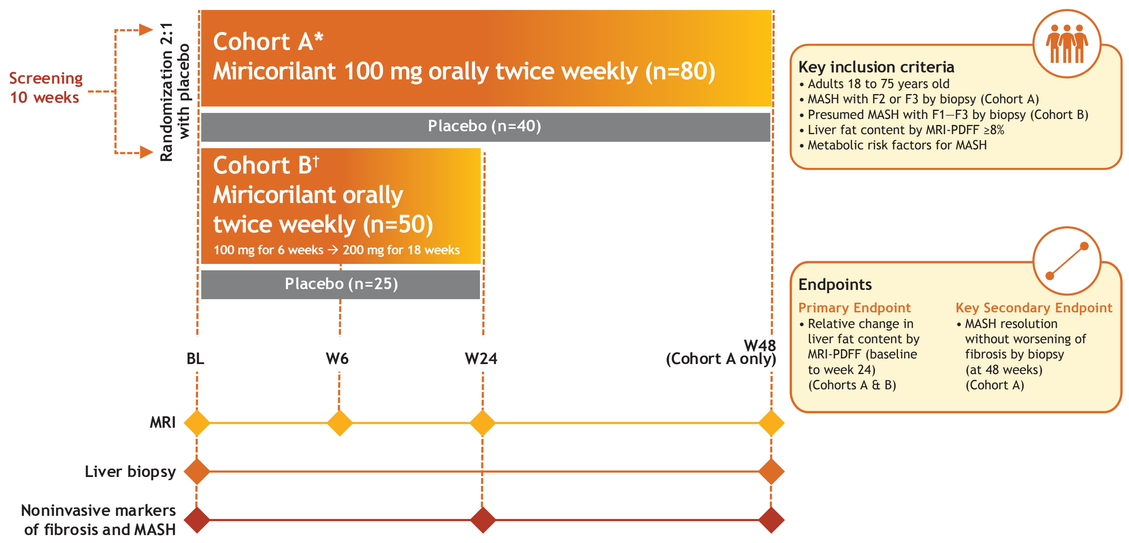
ALT, alanine aminotransferase; AST, aspartate aminotransferase; FFA, free fatty acid; GR, glucocorticoid receptor; LFC, liver fat content; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MR, mineralocorticorticoid receptor; NAS,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

Summary & Conclusions

- Miricorilant, an oral, nonsteroidal selective glucocorticoid receptor modulator (SGRM), may offer a promising new strategy for the treatment of MASH
- Previous clinical trials have shown that twice-weekly miricorilant 100 mg was safe, well tolerated, effectively lowered liver fat, and improved other 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 or presumed noncirrhotic MASH
- MONARCH is actively enrolling at sites across the United States, Mexico, and India

MONARCH Study Design

A phase 2b, double-blind, placebo-controlled study evaluating miricorilant in patients with biopsy-confirmed or presumed non-cirrhotic MASH



Primary objective: To assess the efficacy of miricorilant compared to placebo in reducing liver fat content

*Stratification for Cohort A includes presence or absence of T2DM and fibrosis stage F2 vs F3.
†Stratification for Cohort B includes presence or absence of T2DM and fibrosis stage F1 vs F2–3.

- MONARCH (NCT06108219) is a phase 2b, double-blind, placebo-controlled, randomized study evaluating miricorilant in patients with biopsy-confirmed or presumed noncirrhotic MASH
- **Cohort A:** Approximately 120 adults with liver biopsy-confirmed MASH (F2 or F3 by biopsy) are being randomized 2:1 to miricorilant 100 mg or placebo twice weekly for 48 weeks
- **Cohort B:** Approximately 75 adults with presumed MASH with F1–F3 by biopsy are being randomized 2:1 to miricorilant 100 mg or placebo twice weekly for 6 weeks, followed by dose escalation to miricorilant 200 mg or placebo twice weekly for 18 weeks

Endpoints

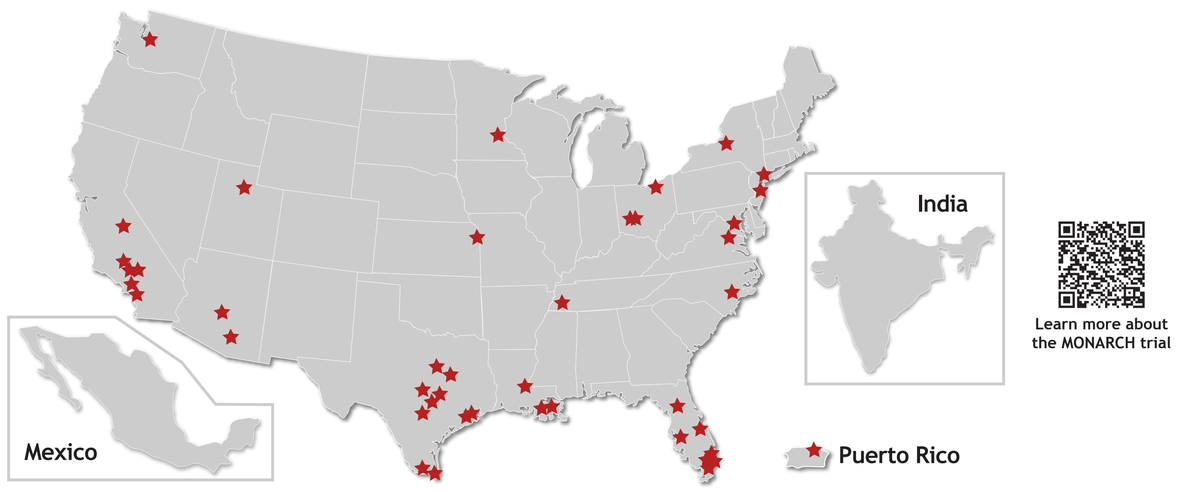
- **Primary endpoint in Cohort A & B:** Change from baseline in LFC at week 24, assessed by MRI-PDFF
- **Key secondary endpoint in Cohort A:** Resolution of steatohepatitis and no worsening of liver fibrosis at week 48, assessed by biopsy
- **Other secondary and exploratory endpoints:** Changes in liver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

ALT, alanine transaminase; AST, aspartate aminotransferase; BL, baseline; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ELF, enhanced liver fibrosis; HDL, high-density lipoprotein; LFC, liver fat content; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAS, nonalcoholic fatty liver disease activity score; NASH-CRN, NASH Clinical Research Network; SBP, systolic blood pressure; ULN, upper limit of normal; W, week.

Key Inclusion and Exclusion Criteria

Inclusion	Exclusion
• 18—75 years old	
• Stable body weight	• BMI <18 kg/m² or >45 kg/m² • 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 MASLD, resmetirom
• **Cohort A:** Histological diagnosis of MASH ○ NAS ≥4 ○ NASH-CRN fibrosis score 2 or 3 • **Cohort B:** A liver biopsy result that does not meet the criteria for inclusion in Cohort A and either ○ NAS ≥3 and NASH-CRN fibrosis score of 1 OR ○ NAS ≥2 and NASH-CRN fibrosis score of 2 or 3	• Cirrhosis • Hepatic decompensation • Any other chronic liver disease
• 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 m² ○ Creatine kinase >3× ULN
• Risk factors for MASH: ○ Type 2 diabetes OR ○ Presence of ≥2 components of metabolic syndrome based on the following: ○ Fasting blood glucose ≥100 mg/dL ○ SBP ≥130 mm Hg or DBP ≥85 mm Hg ○ Serum triglycerides ≥150 mg/dL ○ Serum HDL <40 mg/dL (men) or <50 mg/dL (women) ○ Overweight or obese	• Type 1 diabetes

MONARCH Trial Sites



Learn more about the MONARCH trial

Site map as of 12/02/2024. Additional sites to be opened.

References

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Presenter Disclosures

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