Background

- Cortisol, a hormone that regulates metabolism and stress, has been implicated in the development and progression of NAFLD (also known as MASH). Cortisol can contribute to excess FFAs in the liver by increasing FFA uptake and de novo lipogenesis.
- Cortisol has affinity for the GR (6-fold affinity for GR vs NIH) and 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 NASH-CRN (also known as MASH). Cortisol activity in the liver.

**Miricorilant (CORT118335)**

- An orally administered, nonsteroidal SGRM that acts as a mixed agonist/antagonist of the GR and a modest antagonist of the MR.
- Has high affinity for the GR and NIH (6-fold affinity for GR vs NIH).

**Study Design**

**Randomization 2:1**

<table>
<thead>
<tr>
<th>Stratification factors</th>
<th>Miricorilant 100 mg orally twice weekly (n=100)</th>
<th>Placebo (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>BL</td>
<td>W6</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>W24</td>
<td>W48</td>
</tr>
</tbody>
</table>

**Inclusion & Exclusion Criteria**

**Inclusion**

- 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
- Histological diagnosis of NASH/MASH
  - NAS ≥4
  - NASH-CRN fibrosis score ≥ 3
- AST >17 U/L (women) and >20 U/L (men)
- 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
    - HDL cholesterol <40 mg/dL (men) or <50 mg/dL (women)
    - Overweight or obese

**Exclusion**

- ≥5% weight change within 3 months of screening
- MRI/PDFF with ≥8% steatosis within 6 weeks of baseline
- Fibroscan liver stiffness measurement ≥8 kPa
- Other chronic liver disease
- Cushing’s syndrome
- Hepatic decompensation
- Significant alcohol consumption
- Use of drugs associated with NASH/MASLD, resiquimod, pioglitazone, high-dose vitamin E, GLP-1 agonists
- AST >5 ULN
- ALT >5 ULN
- eGFR <60 mL/min/1.73 m²
- Serum creatinine >1.2 mg/dL
- Type 1 diabetes

**Endpoints**

- **Primary endpoint:** Change from baseline in LFC at week 24, assessed by MRI-PDFF
- **Secondary endpoints:** 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

**Study Design**

**Miricorilant 100 mg orally twice weekly (n=100)**

**Placebo (n=50)**

**BL**

**W6**

**W24**

**W48**

**MRI**

**Liver biopsy**

**Noninvasive markers of fibrosis and NASH**

**References**

2. Pinetella AL et al., Hepatology. 2023; ePub.
5. Allhoff N et al., AASLD 2021; Abstract 5015.

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