Miricorilant, a selective GR modulator, induced a rapid and significant reduction in liver fat content in a randomized, placebo-controlled phase 2a study in patients with non-alcoholic steatohepatitis

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Summary & Conclusions

- Treatment with miricorilant resulted in large, rapid reductions in liver fat content (LFC).
- One patient experienced complete radiologic resolution of fatty liver upon treatment with miricorilant 600 mg for 34 days.
- The LFC reductions were accompanied by significant increases in serum aminotransferases that resolved upon discontinuation of miricorilant.
- Similarly, miricorilant led to a rapid reduction in liver triglycerides in a mouse study. Aminotransferase elevations observed in this model were transient.
- A phase 1b study to evaluate if lower doses of miricorilant reduce hepatic fat content without causing liver irritation in patients with NASH is ongoing.

The authors want to thank all those who participated in this study: The study patients and their families, the investigators, and the sponsor team.

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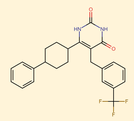
Background

- Non-alcoholic fatty liver disease (NAFLD) has a global prevalence of about 25%[1,2] but no approved pharmacologic treatments.[3]
  - More than a quarter of adults with NAFLD are presumed to have nonalcoholic steatohepatitis (NASH).[1]
- Both the glucocorticoid (GR) and mineralocorticoid receptor (MR) have been implicated in the development and progression of NAFLD.
- GR and MR antagonists have shown beneficial effects in preclinical models.
  - In mice fed a high-fat diet, the GR antagonist mifepristone reduced liver injury, improved insulin sensitivity, and increased plasma adiponectin concentrations.[4]
  - In rodent models, the MR antagonist spironolactone improved hepatic steatosis (by reducing hepatic inflammation and insulin resistance[5]) and liver fibrosis[6].
- **Miricorilant** (CORT118335, Corcept Therapeutics) is an investigational selective GR modulator that acts as a mixed agonist/antagonist of the GR and an antagonist of the MR in preclinical models.
  - Miricorilant had a robust hepatic lipid-lowering effect resulting from a unique combination of GR-dependent stimulation of lipid efflux from the liver with a lack of stimulation of GR-dependent hepatic fatty acid uptake in nonclinical studies.[7]
- This phase 2a study assessed the safety and efficacy of miricorilant in reducing liver fat content in patients with presumed NASH.

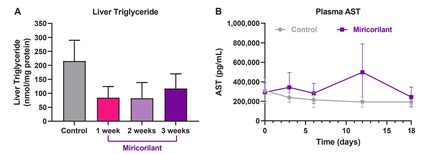


Premise

- Miricorilant's high activity in liver tissue and direct effect on hepatocytes[7] make it well-suited for development as a potential NASH treatment.
  - In mice on a "fast food diet," miricorilant successfully prevented weight gain, liver steatosis, and adipocyte hypertrophy.[8]
  - In mouse models of NAFLD, miricorilant reversed and prevented liver steatosis by preventing hepatic lipid accumulation.[7]
  - Two studies in mice using an amylin liver NASH model have shown reductions in fibrosis stage and NAFLD score with miricorilant.

1 Liver Effects of Miricorilant in a Mouse Model

- In mice on a high-fat diet, daily dosing of miricorilant led to a rapid reduction in liver triglycerides starting at week 1 (A).
- Aspartate aminotransferase (AST) showed a transient increase at 2 weeks but normalized by 3 weeks without a change in miricorilant dose (B).



Male C57 mice (n=24) were given a diet containing 60% fat for 3 weeks. Miricorilant (60 mg/kg) was administered once a day via oral gavage. Plasma AST was measured on days 3, 7, 12, and 18; 6 mice were sacrificed each week at weeks 1, 2, and 3 for assessment of liver triglycerides. The control group (high-fat diet only) was terminated after 3 weeks.

References

(1) Younossi ZM et al., *Hepatology* 2016;64(1):73-84.
(2) Mitra S et al., *Transl Gastroenterol Hepatol* 2020;5:16.
(3) Konerman MA et al., *J Hepatol* 2018;68(2):362-375.
(4) Hashimoto T et al., *PLoS One* 2013;8(11):e79724.
(5) Wada T et al., *Endocrinology* 2010;151(5):2040-2049.
(6) Fujisawa G et al., *Transl. Res.* 2006;148(3):149-156.
(7) Koorneef LL et al., *Endocrinology* 2018;159(12):3925-3936.
(8) Mammi C et al., *Int J Obes* 2016;40(6):964-972.

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2 Phase 2 Study Design

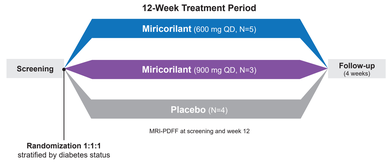
- Double-blind, multi-center, placebo-controlled, randomized 3-arm phase 2a study (NCT03823703)
- Planned enrollment: 120; actual enrollment: 12
  - The study was suspended due to elevated liver transaminases.

Primary endpoint

- Relative change in liver fat content (LFC) from baseline to week 12 (by MRI-PDFF)

Secondary & exploratory endpoints

- Change in LFC for both dose levels of miricorilant combined
- Proportion of patients with relative reduction in LFC ≥30% and ≥50%
- Changes in NASH biomarkers (eg, AST, ALT, GGT)
- Safety and tolerability of miricorilant



Patient Population

- Adults (18-75 yrs) with presumed NASH with fibrosis based on
  - Historical liver biopsy showing NASH, NAFLD Activity Score (NAS) ≥4 and F1-F3 fibrosis OR all of the following:
    - AST >17 U/L (women) / AST >20 U/L (men) AND
    - FibroScan liver stiffness ≥8.5 kPa AND
    - Controlled Attenuation Parameter (CAP) ≥300dB/m

  AND
  - MRI-PDFF with ≥10% steatosis

  AND
  - Presence of 2+ components of metabolic syndrome
- Have not had weight loss ≥10% in the last 6 months
- Consistent ALT and AST baseline measurements not >5x ULN

ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; ULN, upper limit of normal.

3 Baseline Characteristics

	Miricorilant 600 mg (N=5)	Miricorilant 900 mg (N=3)	Placebo (N=4)	Overall (N=12)
Age (years) median (Q1, Q3)	58.0 (51.0, 67.0)	61.0 (39.0, 67.0)	43.5 (32.0, 54.5)	54.5 (39.0, 64.0)
Female, n (%)	2 (40.0%)	2 (66.7%)	2 (50.0%)	6 (50.0%)
Weight (kg)	103.0 (14.72)	107.7 (33.71)	111.5 (18.71)	107.0 (19.89)
BMI (kg/m²)	37.4 (4.44)	39.6 (7.98)	39.3 (5.51)	38.6 (5.30)
Liver fat* (%)	15.7 (6.54)	24.6 (6.04)	19.9 (8.75)	19.3 (7.53)
NASH biomarkers				
ALT (U/L)	33.2 (15.94)	52.3 (15.63)	54.0 (12.11)	44.9 (16.86)
AST (U/L)	25.6 (12.76)	35.7 (8.14)	31.0 (4.08)	29.9 (9.68)
GGT (U/L)	26.2 (9.20)	52.7 (19.63)	59.0 (50.29)	43.8 (32.20)
Lipids				
HDL (mg/dL)	35.52 (5.79)	55.21 (10.54)	38.61 (7.10)	41.31 (10.77)
Triglyceride (mg/dL)	158.41 (70.18)	103.54 (12.83)	152.21 (59.56)	142.48 (57.79)
Cholesterol (mg/dL)	180.31 (47.26)	221.62 (29.19)	167.95 (34.63)	186.49 (42.12)
HbA1c (%)	6.3 (1.3)	5.9 (1.4)	5.3 (0.6)	5.9 (1.1)
Serum insulin (mIU/L)	23.2 (7.61)	63.5 (7.71)	45.3 (19.80)	40.0 (20.56)

Values shown are mean (SD) unless labeled otherwise. HDL, high-density lipoprotein.
*Liver fat measured by MRI-PDFF.

Disclosures

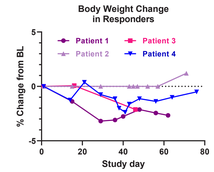
KK: Consultant/Advisor for Gilead, Intercept, Madrigal, NGM; Promotional Speaker for Abbvie, Gilead, Intercept; Investigator/Researcher for Gilead, Madrigal, NGM, Viking, Enanta, Metacrine, Diapharma, Intercept. **PB:** Employee of Radius Health; Consultant for Corcept. **SC, RAJ, and ML:** No conflicts to disclose. **ALH and BG:** Employees of Corcept. **JK:** Financial support by Corcept. **AM:** Investigator/Researcher for Corcept, NovoNordisk, Viking, Madrigal, Pfizer, Akero, North Sea.

4 Reduction in Liver Fat Content

- Post-baseline MRI-PDFF results were available in 7 patients.
- Rapid, large reductions in LFC were observed in 4 miricorilant-treated patients (duration of treatment: 30-44 days).
  - All responders experienced ≥30% relative reduction in LFC, 2 experienced ≥50% relative reduction in LFC, and 1 experienced complete resolution of fatty liver.
  - Hepatic fat reduction was independent of changes in weight and other metabolic parameters.

	Dose (mg)	Age (yrs)	Sex	Days on treatment	Liver fat (%) BL	Liver fat (%) Follow-up	Relative change from BL in % liver fat
Patient 1	900	61	F	30	17.6	6.1	-65.3
Patient 2	900	67	F	44	28.3	15.0	-47.0
Patient 3	900	39	M	31	27.8	17.1	-38.5
Patient 4	600	58	F	34	12.6	3.3*	-73.8
Patient 5	600	51	M	39	17.9	22.9	27.9
Patient 6	Placebo	25	F	67	10.7	10.8	0.9
Patient 7	Placebo	39	M	59	27.6	29.9	8.3

* Complete resolution of fatty liver (<5% liver fat). BL, baseline.

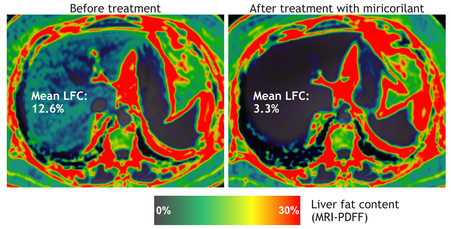


Change in Liver Volume in Responders

	Dose (mg)	Liver volume (mL) BL	Liver volume (mL) Follow-up	Percent change from BL in liver volume (%)
Patient 1	900	1606	1303	-18.9
Patient 2	900	1675	1314	-21.6
Patient 3	900	3857	3113	-19.3
Patient 4	600	1899	1505	-20.7

Liver Imaging in Patient 4

- The patient with the largest reduction in LFC and complete resolution of fatty liver

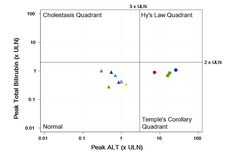


5 Adverse Events (occurring in ≥2 patients)

	Miricorilant 600 mg (N=5)	Miricorilant 900 mg (N=3)	Placebo (N=4)
ALT increased	1 (20.0%)	3 (100.0%)	0 (0.0%)
AST increased	1 (20.0%)	2 (66.7%)	0 (0.0%)
Headache	2 (40.0%)	1 (33.3%)	0 (0.0%)
Abdominal distension	1 (20.0%)	1 (33.3%)	0 (0.0%)
Influenza-like illness	0 (0.0%)	2 (66.7%)	0 (0.0%)
Drug-induced liver injury	0 (0.0%)	2 (66.7%)	0 (0.0%)

Liver Test Abnormalities

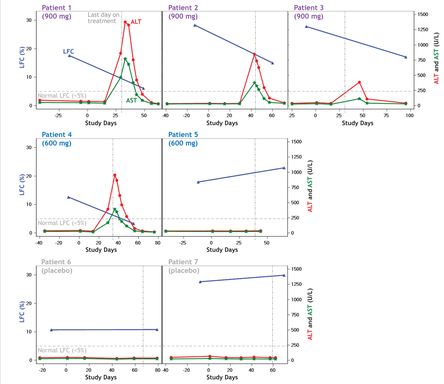
- Elevated serum aminotransferase levels (>5x ULN) were observed at around 4 weeks in the patients with reduction in LFC, leading to suspension of the trial.
  - Increases were accompanied by nausea and vomiting (1 patient) and worsening abdominal distension (1 patient).
  - No conclusive evidence for an etiology other than study drug exposure was found.
  - No increases were observed in patients without reduction in LFC.
- Liver enzyme increases did not meet the definition of Hy's Law and resolved in all patients upon discontinuation of miricorilant.



Patients with reduction in LFC shown as circles.

Time Course of Aminotransferase Levels and LFC

(In patients with post-baseline MRI)



6 Phase 1b Dose-Ranging Study

- Open-label study in patients with presumed NASH (NCT05117489)
  - To assess the safety and tolerability of miricorilant
  - To assess the efficacy of miricorilant in reducing liver fat content
- Currently recruiting (target: approx. 26 patients; 5 US sites)
- Cohort 1: Dose escalation
  - Miricorilant may be better tolerated when titrated
  - Miricorilant titrated from 150 mg to 600 mg or highest tolerated dose
  - MRI-PDFF at week 2, 4, 8, 12, and 16; safety review every 4 weeks
- Cohorts 2-4: Fixed dose
  - Test higher doses based on tolerability (after enrollment in cohort 1 has completed)