Poster #48

MIRICORILANT REDUCED LIVER FAT AND CARDIOMETABOLIC DISEASE MARKERS IN A PHASE 1B, OPEN-LABEL DOSE-FINDING STUDY IN PATIENTS WITH NON-ALCOHOLIC STEATOHEPATITIS (NASH)

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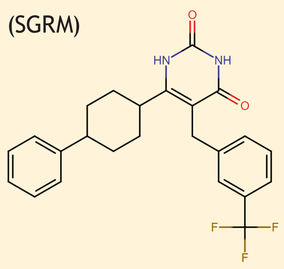
Background

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

Miricorilant (CORT118335)

- An oral, nonsteroidal selective GR modulator (SGRM)
- Acts as a mixed agonist/antagonist of the GR and a modest antagonist of the MR[3]
- May improve hepatic steatosis by selectively modulating cortisol activity in the liver
- Reversed and prevented liver steatosis by preventing hepatic lipid accumulation, and showed reductions in inflammation and fibrosis stage and NAS in preclinical models of NAFLD/MASLD and NASH/MASH[4]



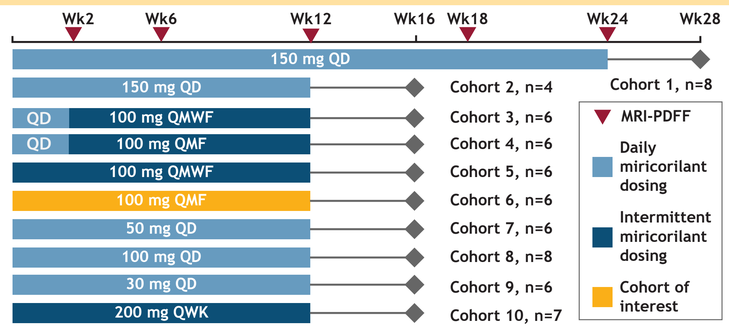
Phase 2a Study of Miricorilant in Patients With Presumed NASH/MASH (NCT03823703)

- A double-blind, multi-center, placebo-controlled, randomized 3-arm phase 2a study to assess the safety and efficacy of miricorilant in reducing LFC in patients with presumed NASH/MASH
  - Adult patients (18–75 years) with presumed NASH/MASH were randomized 1:1:1 to miricorilant 600 mg or 900 mg QD or placebo for 12 Wks
- Miricorilant treatment for 30–44 days resulted in large, rapid reductions in LFC in 4 patients (–39% to –74% reduction)[5]
- These 4 patients experienced concurrent elevations in serum ALT and AST levels (>5× ULN), leading to early study termination by the sponsor
  - No significant change in ALP or bilirubin levels occurred
  - No patient met Hy's Law criteria
  - Transaminase elevations resolved rapidly in all patients upon discontinuation of miricorilant

⇨ The phase 1b, open-label trial reported here evaluated if significantly lower doses and intermittent dosing of miricorilant could gradually reduce LFC without a corresponding rise in liver enzymes

ALP, alkaline phosphatase; 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; QD, every day; SGRM, selective glucocorticoid receptor modulator; ULN, upper limit of normal; Wk, week.

Phase 1b, Open-Label Trial of Miricorilant in Patients With Presumed NASH/MASH (NCT05117489)



Key eligibility criteria

- Adults 18–75 years old
- Presumed NASH/MASH with fibrosis
- LFC by MRI-PDFF ≥8%
- AST <5× ULN, ALT <5× ULN
- eGFR >60 mL/min/1.73 m^2

Endpoints

- Primary: Relative change in LFC from BL by MRI-PDFF
- Secondary: Change from BL in AST, ALT, GGT; change from BL in ELF score

BL, baseline; eGFR, estimated glomerular filtration rate; ELF, enhanced liver fibrosis; GGT, gamma-glutamyl transferase; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; QMWF, every Monday, Wednesday, Friday; QMF, every Monday and Friday; QWK, once weekly.

Results: All Cohorts in Phase 1b Study

Baseline Characteristics

Dosing Schedule		150 mg QD x24 Wk	150 mg QD x12 Wk	100 mg QD x2 Wk, QMWF	100 mg QD x2 Wk, QMF	100 mg QMWF	100 mg QMF	50 mg QD	100 mg QD	30 mg QD	200 mg QWK
Cohort	**Total (n=63)**	**Cohort 1 n=8**	**Cohort 2 n=4**	**Cohort 3 n=6**	**Cohort 4 n=6**	**Cohort 5 n=6**	**Cohort 6 n=6**	**Cohort 7 n=6**	**Cohort 8 n=8**	**Cohort 9 n=6**	**Cohort 10 n=7**
Age (years), mean (SD)	51.3 (12.57)	56.3 (9.88)	49.3 (6.55)	48.7 (22.35)	54.0 (16.49)	55.2 (10.30)	56.3 (10.13)	44.8 (9.37)	49.6 (8.03)	52.8 (15.43)	45.7 (12.61)
Female sex, n (%)	38 (60.3)	5 (62.5)	2 (50.0)	4 (66.7)	3 (50.0)	5 (83.3)	4 (66.7)	4 (66.7)	4 (50.0)	2 (33.3)	5 (71.4)
Ethnicity											
Hispanic or Latino	36 (57.1)	2 (25.0)	3 (75.0)	5 (83.3)	4 (66.7)	4 (66.7)	3 (50.0)	5 (83.3)	3 (37.5)	3 (50.0)	4 (57.1)
White	56 (88.9)	6 (75.0)	4 (100)	6 (100)	5 (58.3)	6 (100)	6 (100)	6 (100)	5 (62.5)	6 (100)	6 (85.7)
BMI (kg/m^2), mean (SD)	38.1 (6.6)	39.4 (5.2)	35.2 (5.6)	39.1 (6.1)	37.6 (9.8)	38.8 (8.7)	40.6 (7.4)	35.3 (4.7)	35.9 (7.3)	38.6 (3.5)	39.5 (7.4)
LFC per MRI-PDFF (%), mean (SD)	19.08 (7.76)	16.53 (5.9)	21.30 (9.5)	19.02 (11.4)	16.23 (4.4)	20.08 (6.5)	22.83 (10.9)	19.73 (5.1)	18.74 (7.4)	15.94 (6.5)	21.20 (10.3)
FibroScan® liver stiffness (kPA), mean (SD)	12.06 (5.27)	16.55 (9.67)	10.50 (1.54)	12.40 (6.61)	11.60 (3.47)	13.92 (7.09)	11.12 (3.40)	11.48 (3.83)	9.85 (1.18)	10.18 (0.37)	10.65 (2.05)
ALT (U/L), mean (SD)	53.9 (30.4)	51.5 (35.0)	47.5 (14.8)	48.7 (30.0)	67.7 (33.5)	33.0 (7.8)	54.0 (36.2)	61.0 (28.8)	55.5 (30.2)	60.3 (38.5)	57.4 (37.1)
AST (U/L), mean (SD)	36.7 (15.5)	36.5 (16.6)	34.5 (15.2)	39.0 (21.9)	47.3 (17.4)	25.0 (7.4)	35.3 (17.2)	35.2 (10.3)	35.5 (14.3)	37.5 (15.9)	40.0 (16.5)
HbA1c (%), mean (SD)	6.28 (0.95)	6.24 (0.79)	5.93 (0.21)	5.85 (0.64)	6.68 (0.71)	6.83 (1.49)	6.48 (0.68)	6.32 (1.22)	6.0 (1.44)	6.08 (0.77)	6.33 (0.67)
Fasting glucose (mg/dL), mean (SD)	125.3 (30.3)	133.3 (26.2)	106.3 (9.3)	115.2 (18.0)	133.2 (35.0)	152.2 (46.0)	123.8 (41.4)	117.8 (28.2)	108.5 (20.0)	128.0 (26.9)	129.6 (27.1)

BMI, body mass index; HbA1c, hemoglobin A1c; SD, standard deviation.

Change in Liver Parameters From BL to Wk 12

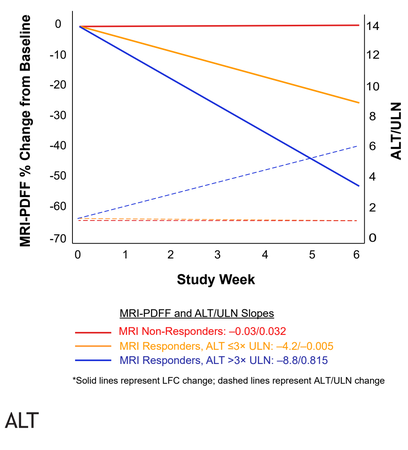
- Best benefit-risk profile at Wk 12 observed with miricorilant 100 mg twice weekly (mean % change from baseline = -28.2%)
- Greatest reductions in LFC by Wk 6 occurred in patients receiving daily miricorilant 50–150 mg (mean % change from BL = –22.3%)
  - However, these patients were more likely to interrupt or discontinue study drug prior to Wk 12 due to concurrent transaminase elevation
- No significant changes in body weight were observed in any cohort

Dosing Schedule		150 mg QD x24 Wk	150 mg QD x12 Wk	100 mg QD x2 Wk, QMWF	100 mg QD x 2Wk, QMF	100 mg QMWF	100 mg QMF	50 mg QD	100 mg QD	30 mg QD	200 mg QWK
Cohort*	**Total (n=56)**	**Cohort 1 n=7**	**Cohort 2 n=4**	**Cohort 3 n=5**	**Cohort 4 n=6**	**Cohort 5 n=6**	**Cohort 6 n=5**	**Cohort 7 n=6**	**Cohort 8 n=6**	**Cohort 9 n=5**	**Cohort 10 n=6**
LFC per MRI-PDFF (%), mean (SD)	-13.17 (23.6)	-16.7 (18.8)	-40.1 (29.7)	4.67 (23.4)	5.8 (24.6)	-17.2 (26.7)	-28.2 (13.5)	-16.5 (22.5)	-20.3 (23.8)	-5.4 (9.9)	-4.5 (17.6)
Responders,† n (range of LFC %)	19 (-30, -77)	5 (-36, -70)	2 (-51, -77)	1 (-35)	0	2 (-40, -59)	2 (-37, -43)	3 (-30, -54)	3 (-51, -70)	0	1 (-35)
ALT (U/L), mean (SD)	-5.5 (25.7)	-9.0 (30.0)	6.0 (21.0)	-17.8 (31.0)	-5.2 (11.8)	3.2 (12.4)	-4.0 (21.4)	-5.7 (34.1)	-13.3 (22.1)	-4.4 (37.1)	-1.7 (35.3)
AST (U/L), mean (SD)	-2.2 (15.5)	-6.0 (12.4)	5.3 (13.8)	-9.6 (26.3)	-3.2 (16.6)	2.0 (5.5)	-6.0 (7.2)	-0.3 (15.7)	-7.7 (12.7)	-1.6 (20.2)	6.8 (20.85)
GGT (U/L), mean (SD)	-0.7 (18.1)	-2.9 (11.1)	8.3 (17.6)	-3.2 (14.9)	2.2 (19.6)	-7.0 (18.4)	0.4 (16.9)	1.5 (17.8)	-8.3 (24.1)	-3.2 (16.3)	8.2 (27.6)
ALP (U/L), mean (SD)	0.5 (6.6)	0.3 (4.8)	-3.0 (12.1)	-2.6 (6.7)	0.5 (5.5)	-1.7 (8.8)	2.2 (4.8)	5.8 (3.8)	3.2 (3.1)	1.6 (2.3)	-2.2 (10.2)
Bilirubin (mmol/L), mean (SD)	-0.4 (3.0)	-0.5 (2.3)	1.5 (2.2)	-2.0 (1.3)	1.7 (3.2)	-0.8 (4.1)	-0.3 (1.1)	-2.9 (4.0)	-1.0 (2.5)	-0.7 (2.9)	1.3 (2.7)

*Numbers reflect patients who completed Wk 12; some patients discontinued prior to Wk 12 due to elevations in liver function tests. For cohort 1, n=7 for LFC and n=8 for ALT, AST, GGT, ALP, and bilirubin.
†Responders are defined as patients who had ≥30% reduction in LFC from BL at any time.

Change in LFC in Responders With or Without ALT >3× ULN

- Non-responders did not experience a rise in transaminase levels
- Responders without ALT >3× ULN had a mean reduction in LFC of -25.5% at Wk 6
- Responders with ALT >3× ULN had a faster decline in LFC loss, mean reduction in LFC of -52.6% at Wk 6
  - Responders with ALT >3× ULN slope -8.76; responders without ALT >3× ULN slope -4.24
  - Patients with a more gradual weekly rate of LFC loss were less likely to have a corresponding rise in ALT



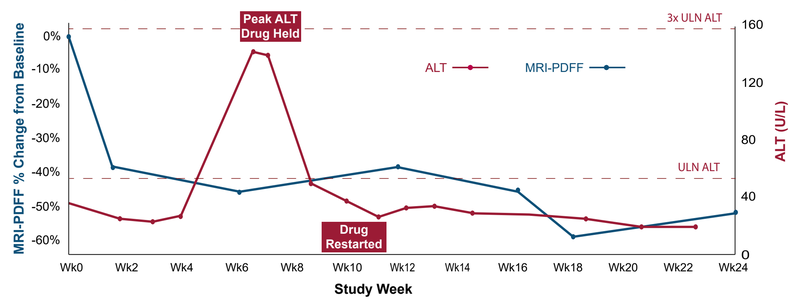
*Solid lines represent LFC change; dashed lines represent ALT/ULN change

ALT and LFC Profiles in Patients With Drug Held Due to ALT or AST Elevation and Restarted at the Same Dose

	Patient 1 (Cohort 1; 150 mg QD x 24 Wk)	Patient 2 (Cohort 1; 150 mg QD x 24 Wk)	Patient 3 (Cohort 2; 150 mg QD x 12 Wk)
BL ALT (U/L)	18	30	49
Peak ALT (U/L)	190 (U1, Wk 5)	142 (Wk 6)	95 (Wk 4)
End of treatment ALT (U/L)	15 (Wk 24)	18 (Wk 24)	67 (Wk 12)
Wks off miricorilant	7 Wks	4 Wks	3 Wks
Wks on miricorilant after rechallenge	11 Wks	13 Wks	4 Wks
Maximum % LFC reduction	-40.4%	-45.9%	-22.9%

*U1, unscheduled visit.

Patient 2: ALT and LFC Profile



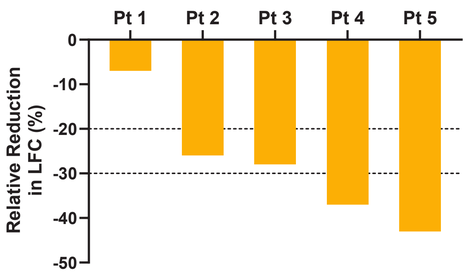
Safety: Miricorilant Was Overall Well-tolerated

- Treatment-emergent adverse events (TEAEs) occurred in 82.5% (n=52) of patients
  - TEAEs experienced by ≥5% of the total population were headache (15.9%), increased ALT (9.5%), increased AST (7.9%), COVID-19 (7.9%), increased transaminases (6.3%), upper abdominal pain (6.3%), constipation (6.3%), diarrhea (6.3%), and nausea (6.3%)
- 4.8% (n=3) of patients had grade ≥3 TEAEs
- Two serious adverse events (AEs) occurred (myocardial infarction; polysomy aneuploidy of chromosomes 3, 7, and 17); neither was considered related to miricorilant
- Liver transaminase AEs were mostly grade 1–2, with a grade 3 ALT and AST increase in 1 patient in cohort 8 (miricorilant 100 mg QD)
  - These AEs were associated with rapid reduction in liver fat; ALT & AST levels returned to BL rapidly upon miricorilant discontinuation
- TEAEs leading to drug interruption or discontinuation occurred in 22.2% of patients (n=14)
  - All but one was due to transaminase elevation in setting of rapid drop in LFC (up to -70.2%), generally within 6 Wks of treatment
  - Patients who restarted miricorilant did not have a secondary rise in ALT, indicating ALT increase was transient
- No patient met Hy's Law criteria

Results: Cohort 6 (100 mg Twice Weekly) Had the Best Benefit-Risk Profile

- At Wk 12, mean relative reduction in LFC was –28.2% (SD, 13.5), with corresponding decline in liver enzymes
- Patients in this cohort overall had improved lipid profiles, glycemic markers, and fibrosis biomarkers

Reduction in LFC from BL to Wk 12



*Data shown for the 5 patients in cohort 6 who received ≥1 dose of study drug, remained on trial for ≥6 Wks, and had a 12 Wk MRI-PDFF assessment. One patient discontinued at Wk 6 (lost to follow-up) and is not included.

Cardiometabolic Disease & Fibrosis Markers

Mean change and mean % change from BL	Cohort 6
Liver enzymes	
ALT (U/L)	-4.0 (-5.7%)
AST (U/L)	-6.0 (-16.7%)
Glycemic markers	
Fasting glucose (mg/dL)	-6.8 (-2.6%)
Insulin (mIU/L)	-5.4 (-17.9%)
HOMA-IR	-1.9 (-19.6%)
Lipid profiles	
LDL (mg/dL)	-9.8 (-4.3%)
VLDL (mg/dL)	-4.0 (-5.8%)
Triglycerides (mg/dL)	-20.8 (-6.4%)
Fibrosis markers	
ELF score	-0.2 (-1.8%)

HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoproteins; pt, patient; VLDL, very low-density lipoproteins.

Summary & Conclusions

- Miricorilant, a nonsteroidal selective GR modulator (SGRM), may offer a promising new strategy for treating NASH/MASH
- Miricorilant 100 mg twice weekly was safe, well-tolerated, and resulted in reduced LFC and improved hepatic, lipid, and glycemic markers
  - This dosing schedule provided a gradual reduction in liver fat of ~30% over 12 Wks without an associated rise in hepatic transaminase levels
  - Across all cohorts, responders receiving intermittent miricorilant lost LFC more gradually and were less likely to have a rise in ALT >3× ULN compared to daily dosing
- Patients with drug held due to transaminase elevations did not have a secondary rise in ALT when miricorilant was restarted, indicating ALT increase was transient
- Additionally, miricorilant 150 mg twice weekly is being evaluated in the phase 1b study
- Miricorilant 100 mg twice weekly is being evaluated further in a placebo-controlled phase 2b study (MONARCH, NCT06108219) in patients with biopsy-confirmed NASH/MASH[6]

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Presenter Disclosures

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