Poster #5015-C

Miricorilant Reduced Liver Fat and Cardiometabolic Disease Markers in a Phase 1b, Open-Label Dose-Finding Study in Patients With Non-Alcoholic Steatohepatitis (NASH)

PRESENTER:
Naim Alkhouri, MD, FAASLD
Contact: nalkhouri@azliver.com

Naim Alkhouri,[1] Madhavi Rudraraju,[2] Kris V. Kowdley,[3] Mark Leibowitz,[4] Jacques Benun,[5] Robert A. Jenders,[6] Anita Kohli,[7] Mazen Noureddin,[8] Rashmee Patil,[9] Iulia Cristina Tudor,[10] Jeffrey Botbyl,[10] Joseph M. Custodio,[10] Rafael Mayoral Monibas,[10] Aprille Espinueva,[10] Kavita Juneja,[10] William Guyer,[10] Stephen A. Harrison[2]

[1]Arizona Liver Health, Tucson, AZ; [2]Pinnacle Clinical Research, San Antonio, TX; [3]Liver Institute Northwest, Seattle, WA; [4]Velocity Clinical Research, Santa Ana, CA; [5]Pinnacle Clinical Research, Austin, TX; [6]Velocity Clinical Research, Los Angeles, CA; [7]Arizona Liver Health, Chandler, AZ; [8]Houston Research Institute, Houston, TX; [9]South Texas Research Institute, Edinburg, TX; [10]Corcept Therapeutics Incorporated, Menlo Park, CA

Summary & Conclusions

- Miricorilant, as a selective glucocorticoid receptor modulator (SGRM), may offer a promising new strategy for the treatment of 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 weeks without an associated rise in hepatic transaminase levels
  - Daily miricorilant (50–150 mg) produced greater reductions in LFC by week 6 but was more likely to result in concurrent transaminase elevation requiring study drug interruption or discontinuation
- Additionally, miricorilant 150 mg twice-weekly is being evaluated in the phase 1b study
- Miricorilant 100 mg twice-weekly will be evaluated further in a placebo-controlled phase 2b study (MONARCH) to assess miricorilant's efficacy and safety for the treatment of biopsy-confirmed NASH

LFC, liver fat content.

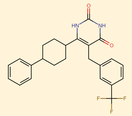
AASLD The Liver Meeting® Nov. 10–14, 2023

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

1 Background

- Cortisol activity has been implicated in the development and progression of NAFLD (also known as 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)



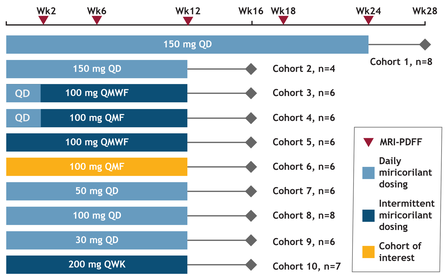
- An oral, nonsteroidal SGRM
- Acts as a mixed agonist/antagonist of the GR and antagonist of the MR[3]
- May improve hepatic steatosis by selectively modulating cortisol activity in the liver
- Reversed and prevented liver steatosis by preventing hepatic lipid accumulation, and showed reductions in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

Phase 2a Study of Miricorilant in Patients with Presumed NASH (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
  - Adult patients (18–75 years) with presumed NASH were randomized 1:1:1 to miricorilant 600 mg daily, miricorilant 900 mg daily, or placebo for 12 weeks
- 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 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 in adults with presumed NASH that is reported here was subsequently conducted to evaluate 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; SGRM, selective glucocorticoid receptor modulator; ULN, upper limit of normal.

2 Phase 1b, Open-label Trial of Miricorilant in Patients with Presumed NASH (NCT05117489)



Key eligibility criteria

- Adults 18–75 years old
- Presumed NASH* with fibrosis
- Liver fat content by MRI-PDFF ≥8%
- AST <5× ULN, ALT <5× ULN
- eGFR >60 mL/min/1.73 m²

Primary endpoint

- Relative change in LFC from baseline by MRI-PDFF

Secondary endpoints

- Change from baseline in AST, ALT, GGT
- Change from baseline in ELF score

*Although the nomenclature has changed to MASH, NASH is used in this poster for consistency with the study protocol. eGFR, estimated glomerular filtration rate; ELF, enhanced liver fibrosis; GGT, gamma-glutamyl transferase; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; QD, every day; QMWF, every Monday, Wednesday, Friday; QMF, every Monday and Friday; QWK, once weekly; Wk, week.

3 Results: All Cohorts

Baseline Characteristics

Dosing Schedule		150 mg QD x 24 Wk	150 mg QD x 12 Wk	100 mg QD x 2 Wk, QMWF	100 mg QD x 2 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/m²), 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; SD, standard deviation.

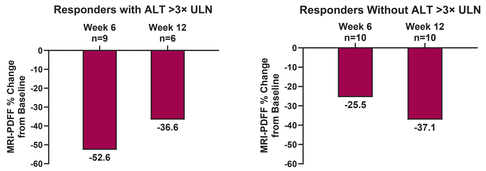
Change in Liver Parameters from Baseline to Week 12

- Greatest reductions in LFC by week 6 occurred in patients receiving daily doses of miricorilant 50–150 mg (mean % change from baseline = −22.3%)
  - However, these patients were more likely to interrupt or discontinue study drug prior to week 12 due to concurrent transaminase elevation
- No significant changes in body weight were observed in any cohort, suggesting that miricorilant is a liver-targeted therapy

Dosing Schedule		150 mg QD x 24 Wk	150 mg QD x 12 Wk	100 mg QD x 2 Wk, QMWF	100 mg QD x 2 Wk, 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 week 12; some patients discontinued prior to week 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 baseline at any time.

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



- Patients with a more rapid weekly rate of LFC loss by week 6 were more likely to experience a corresponding rise in ALT
  - Responders with ALT >3× ULN had a faster decline in LFC loss (slope, −8.76) than responders without ALT >3× ULN (slope, −4.24)
  - Treatment with daily miricorilant was more likely to result in discontinuation of study drug prior to week 12
- 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

Safety

- Overall, miricorilant was well-tolerated
- TEAEs occurred in 82.5% (n=52) of patients, with headache being the most common
- 4.8% (n=3) of patients had grade ≥3 TEAEs
- Two serious 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 1 patient in cohort 8 (miricorilant 100 mg daily) experiencing a grade 3 ALT and AST increase
  - These AEs were associated with rapid reduction in liver fat; ALT and AST levels returned to baseline rapidly upon discontinuation of miricorilant
- TEAEs leading to premature study drug interruption or discontinuation occurred in 22.2% of patients (n=14)
  - All but one was due to rapid drop in liver fat (−16.5% to −70.2%) causing transaminase elevations
  - Patients who restarted miricorilant did not have a secondary rise in ALT, indicating ALT increase was transient
- No patient met Hy's Law criteria

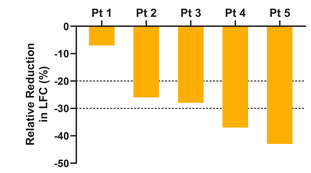
Patients, n (%)	Overall (n=63)
TEAEs experienced by ≥5% of total population	
Headache	10 (15.9)
ALT increased	6 (9.5)
AST increased	5 (7.9)
COVID-19	5 (7.9)
Transaminases increased	4 (6.3)
Abdominal pain, upper	4 (6.3)
Constipation	4 (6.3)
Diarrhea	4 (6.3)
Nausea	4 (6.3)

AE, adverse event; TEAE, treatment-emergent adverse event.

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

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

Reduction in LFC from Baseline to Week 12



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

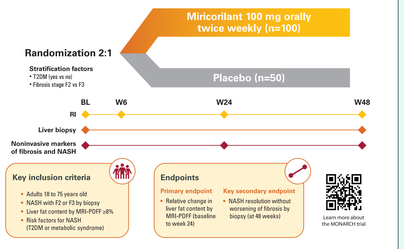
Changes in Cardiometabolic Disease and Fibrosis Markers

Mean change and mean % change from baseline	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.

5 MONARCH Study Design (NCT06108219)

- A phase 2b, double-blind, placebo-controlled, randomized study evaluating miricorilant in patients with biopsy-confirmed noncirrhotic NASH
- Conducted at ~50 sites; currently enrolling



References

(1) Rahimi L et al. *Diabetes Metab Syndr Obes*. 2020;13:1133–1145.
(2) Rinella ML et al. *Hepatology*. 2023, ePub.
(3) Hunt HJ et al. *Bioorg Med Chem Lett*. 2012;22(24):7376–7380.
(4) Koorneef LL, et al. *Endocrinology*. 2018;159(12):3925–3936.
(5) Kowdley KV et al. *Hepatology*. 2021; 74(6)1393A.

Acknowledgements

This study is sponsored by Corcept Therapeutics Incorporated. Medical writing assistance was provided by Valerie Hilliard, PhD, of Corcept Therapeutics Incorporated.

Presenter Disclosures

NA: Grant/research support from 89Bio, AbbVie/Allergan, Akero, Better Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Corcept, DSM, Galectin, Genentech, Genfit, Gilead, Hepagene, Healio, Intercept, Inventiva, Ionis, Madrigal, Merck, NGM, Noom, NorthSea, Novo Nordisk, Perspectum, Pfizer, Poxel, Viking, and Zydus. Speaker's fees from AbbVie/Allergan, Alexion, Echosens, Eisai, Exelixis, Gilead, Intercept, Perspectum, Salix, and Theratechnologies.Consultant for AbbVie/Allergan, Echosens, Fibronostics, Gilead, Intercept, Madrigal, Novo Nordisk, Perspectum, Pfizer, and Zydus.