Effect of Hepatic Impairment on the Pharmacokinetics of Miricorilant: Results From a Phase 1, Open-Label, Adaptive-Design Study

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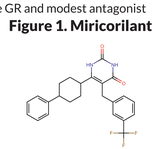
CONCLUSIONS

- **Miricorilant 600 mg was well tolerated in individuals with moderate or severe hepatic impairment and in matched-control healthy volunteers**
- **Hepatic impairment had minimal impact on the total systemic plasma area under the curve (AUC) of miricorilant**
- **These findings support future inclusion of individuals with compensated cirrhotic metabolic dysfunction-associated steatohepatitis (MASH) in the miricorilant clinical development program**

BACKGROUND

- Cortisol activity has been implicated in the development and progression of metabolic dysfunction-associated steatotic liver disease (MASLD)[1,2]
  - Cortisol binding to the glucocorticoid receptor (GR) increases availability of energy substrates, such as free fatty acids (FFAs), that support daytime activities and stress response
  - Cortisol can contribute to elevated lipid levels in the liver by increasing fatty acid uptake and de novo lipogenesis
- Miricorilant (**Figure 1**) is an orally administered, nonsteroidal selective GR modulator that acts as a mixed agonist/antagonist of the GR and modest antagonist of the mineralocorticoid receptor (MR; 6-fold higher affinity for GR vs MR) and may reduce hepatic steatosis by modulating cortisol activity in the liver[3]
- In preclinical models of MASLD/MASH, miricorilant reversed and prevented hepatic steatosis by preventing lipid accumulation in the liver and reduced inflammation, fibrosis stage, and nonalcoholic fatty liver disease activity score[4]
- Miricorilant is primarily eliminated through hepatic metabolism[5]
  - Following a single oral dose of [^{14}C]-miricorilant to healthy volunteers, the majority of the total radioactivity was recovered in the feces, with minimal recovery in the urine

Figure 1. Miricorilant



Miricorilant Clinical Development

- In a phase 1b, multicohort, open-label study (NCT05117489), adults with presumed MASH with fibrosis received miricorilant at doses of 30 to 200 mg daily or intermittently for 12 to 24 weeks[6]
- Miricorilant 100 mg twice weekly demonstrated the best benefit-risk profile at week 12, showing safety, tolerability, a 28.2% reduction in liver fat content (LFC), and improvements in liver enzymes and hepatic, lipid, and glycemic markers[6]
- The ongoing phase 2b MONARCH trial (NCT06108219) is evaluating 100 mg of miricorilant twice weekly and a higher dose of 200 mg twice weekly after a 6-week lead-in of 100 mg in individuals with biopsy-confirmed or presumed noncirrhotic MASH[7]
- Given that miricorilant is primarily eliminated hepatically, the presented phase 1, open-label, single-dose, 1-period, multi-center, adaptive-design study (NCT05553470) assessed the effect of hepatic impairment on miricorilant's pharmacokinetic profile in individuals with or without presumed MASH compared with matched healthy controls

OBJECTIVE

Primary objective:

- Determine the effect of hepatic impairment on miricorilant pharmacokinetics in individuals with moderate (Child-Pugh [CP] class B) and severe (CP class C) hepatic impairment with or without presumed MASH and compared with matched-control healthy volunteers

Secondary objectives:

- Evaluate the safety and tolerability of miricorilant in individuals with normal hepatic function, moderate hepatic impairment, and severe hepatic impairment
- Characterize the pharmacokinetics of the miricorilant metabolite CORT118335-P9 in individuals with normal hepatic function and those with either moderate or severe hepatic impairment

METHODS

- Key inclusion and exclusion criteria are summarized in **Table 1**
- Liver function was assessed at screening, and individuals with hepatic impairment were assigned to the study population according to the CP classification (**Table 2**)
  - Healthy volunteers were included as reference controls and were matched with individuals in the moderate hepatic impairment group based on gender, age (±10 years), and weight (±20%)
  - Those with severe hepatic impairment were reverse matched with the healthy volunteer control group based on gender, age (±10 years), and weight (±20%)

Table 1. Key Inclusion and Exclusion Criteria

Inclusion	Exclusion
All participants	
▪ Nonsmokers or light smokers 18−75 years old ▪ Body weight ≥50.0 kg ▪ eGFR ≥60 mL/min/1.73 m^2	▪ Clinically significant illness or surgery within 4 weeks prior to dosing ▪ Any prior surgery that could affect drug absorption, such as gastric bypass, duodenectomy, or cholecystectomy ▪ Medical condition aggravated by glucocorticoid antagonism and/or mineralocorticoid antagonism ▪ Clinically significant ECG abnormalities or vital sign abnormalities
Participants with hepatic impairment	
▪ BMI ≥18.0 to ≤32 kg/m^2 without presumed MASH; ≥18.0 to ≤40 kg/m^2 with presumed MASH (moderate/severe) ▪ Stable hepatic impairment (CP class B or C) ≥1 month prior to screening ▪ Moderate (7–9 points) or severe (10–15 points) impaired hepatic function assessed by a CP classification score with known medical history of liver disease ▪ For moderate and severe hepatic impairment with presumed MASH, the following MASH risk factors: ○ Type 2 diabetes or ○ ≥2 components of metabolic syndrome (eg, obesity, dyslipidemia, elevated BP, elevated fasting glucose) ▪ ALT ≥43 IU/L (men) and ≥28 IU/L (women) ▪ One of the following: ○ MRI-cT1 value >800 ms ○ MRI PDFF liver fat content ≥8% ○ FibroScan LSM ≥8.5 kPa	▪ Active hepatic encephalopathy Grade 2 or higher ▪ Surgically-created or transjugular intrahepatic portal systemic shunts

ALT, alanine transaminase; BMI, body mass index; BP, blood pressure; CP, Child-Pugh; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; LSM, liver stiffness measurement; MRI-cT1, magnetic resonance imaging corrected T1; PDFF, Proton Density Fat Fraction.

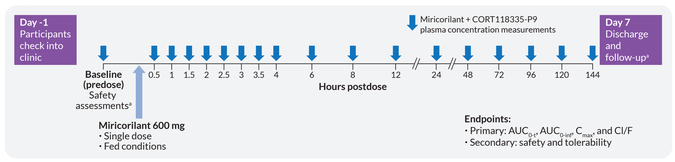
Table 2. Child-Pugh Classification of Severity of Liver Disease

Parameter	1 point	2 points	3 points
Serum albumin, g/L	>35	28–35	<28
Total serum bilirubin, µmol/L	<34	34–51	>51
Prothrombin time,[a] sec prolonged	<4	4–6	>6
Ascites[b]	Absent	Slight	Moderate or participant on medication(s) to control ascites
Hepatic encephalopathy[c]	None	Grade 1 or 2	Grade 3 or 4 or participant receiving medication(s) to prevent encephalopathy

Child-Pugh scoring: mild risk (A or mild) if 5–6 points; moderate risk (B or moderate) if 7–9 points; high risk (C or severe) if 10–15 points.
[a]Expressed as international normalized ratio (INR; <1.7=1 point, 1.7– 2.2=2 points, >2.2=3 points).
[b]Individuals with a history of severe ascites who are receiving diuretics, such as furosemide, to prevent recurrence shall receive the pretreatment point score for the degree of ascites. This reflects the true underlying hepatic pathology.
[c]Encephalopathy is graded as follows:
- Grade 0: normal consciousness, personality, neurological examination, electroencephalogram.
- Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves.
- Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves.
- Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.
- Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity. Encephalogram data if available.

- All participants received a single oral dose of miricorilant 600 mg under fed conditions (**Figure 2**)
- A validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) bioanalytical method was used to determine total plasma concentrations of miricorilant and its metabolite CORT118335-P9 at predose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 48, 72, 96, 120, and 144 hours post-dose
- The primary pharmacokinetic endpoints $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and maximum concentration (C_{max}) were calculated using noncompartmental analyses
  - Analysis of variance (ANOVA) was performed on untransformed elimination rate constant (K_{el}) and elimination half-life ($t_{1/2}$) and on the ln-transformed $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} at the alpha level of 0.05 for (total) miricorilant and its metabolite CORT118335-P9
  - The ratio of geometric means and the corresponding 90% geometric confidence intervals (CIs) were calculated for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}. Time to maximum concentration (T_{max}) was analyzed nonparametrically with point estimates and 90% CIs for the median differences of T_{max} between treatments
- Safety evaluations included adverse events, vital signs, 12-lead electrocardiograms (ECGs), clinical laboratory tests, and physical examinations

Figure 2. Phase 1, Open-Label, Adaptive Design Study Evaluating the Effect of Hepatic Impairment on the Pharmacokinetic Profile of Miricorilant



[a]Adverse events collected and documented until end of study or early termination. Serious adverse events followed for 30 days after drug administration.
AUC, area under the curve; CL/F, apparent clearance; C_{max}, maximum concentration.

RESULTS

- 29 participants were enrolled: 19 individuals with hepatic impairment and 10 healthy volunteers (**Table 3**)
  - Of the participants with hepatic impairment, 5 were diagnosed with presumed MASH
- Baseline demographics are shown in **Table 4**

Table 3. Participant Disposition

	Child-Pugh class B (Moderate hepatic impairment) (n=9)	Child-Pugh class C (Severe hepatic impairment) (n=10)	Matched-control healthy volunteers (n=10)	Total
Screened, n (%)	28	16	10	54
Enrolled,[a] n (%)	9	10	10	29
Dosed, n (%)	9	10	10	29
Completed,[b] n (%)	9 (100)	10 (100)	9 (90)	28 (97)

[a]Twenty-five individuals were not enrolled due to screen failure. [b]Percentage based on the number of dosed participants for a given treatment group or overall, as appropriate.

Table 4. Baseline Demographics and Characteristics

	Child-Pugh class B (Moderate hepatic impairment) (n=9)	Child-Pugh class C (Severe hepatic impairment) (n=10)	Matched-control healthy volunteers (n=10)	Overall (N=29)
Age, years, mean (SD)	62.4 (6.2)	56.4 (12.3)	57.3 (4.2)	58.6 (8.5)
Female, n (%)	2 (22.2)	4 (40.0)	3 (30.0)	9 (31.0)
Ethnicity: Hispanic/Latino, n (%)	9 (100.0)	9 (90.0)	10 (100.0)	28 (96.6)
Race, n (%) White Asian	9 (100.0) 0	9 (90.0) 1 (10.0)	10 (100.0) 0	28 (96.6) 1 (3.4)
BMI, kg/m^2, mean (SD)	29.0 (4.9)	27.4 (5.3)	29.5 (1.3)	28.6 (4.2)

SD, standard deviation.

Safety

- Miricorilant 600 mg was well tolerated
- No grade ≥3 treatment-emergent AEs or laboratory abnormalities were observed, and no new safety concerns were identified (**Table 5**)

Table 5. Safety of Miricorilant in Participants With Hepatic Impairment and Healthy Matched Volunteers

	Child-Pugh class B (Moderate hepatic impairment) (n=9)	Child-Pugh class C (Severe hepatic impairment) (n=10)	Matched-control healthy volunteers (n=10)	Overall (N=29)
At least one TEAE, n (%)	1 (11.1)	2 (20.0)	0	3 (10.3)
TEAE Grade ≥3, n (%)	0	0	0	0
TEAE by severity, n (%) Mild Moderate Severe	1 (11.1) 0 0	2 (20.0) 0 0	0 0 0	3 (10.3) 0 0
TEAEs related to study drug, n (%)	0	0	0	0
TEAEs, n (%) Gastrointestinal disorders Dyspepsia General disorders/ administration conditions Fatigue Nervous system disorders Headache	0 0 0 0 1 (11.1) 1 (11.1)	1 (10.0) 1 (10.0) 1 (10.0) 1 (10.0) 0 0	0 0 0 0 0 0	1 (3.4) 1 (3.4) 1 (3.4) 1 (3.4) 1 (3.4) 1 (3.4)

TEAE, treatment-emergent adverse event.

Pharmacokinetic Parameters

Table 6. Pharmacokinetics of Miricorilant and CORT118335-P9 by Hepatic Function

	Child-Pugh class B (Moderate hepatic impairment) (n=9)	Child-Pugh class C (Severe hepatic impairment) (n=10)	Matched-control healthy volunteers (n=10)
Miricorilant			
$AUC_{0\text{-}t}$, h*ng/mL, geometric mean (G-CV%) [range]	13,679.3 (34.4) [7,103.2–20,787.8]	11,877.0 (50.4) [5,603.3–21,705.0]	11,318.8 (43.1) [5,604.9–20,232.8]
$AUC_{0\text{-}inf}$, h*ng/mL, geometric mean (G-CV%) [range]	14,722.3 (36.1) [7,328.5–22,789.6]	16,443.2 (59.9) [6,466.7–29,601.2]	11,620.5 (44.1) [5,742.0–21,277.4]
C_{max}, ng/mL, geometric mean (G-CV%) [range]	584.3 (32.8) [378.0–876.0]	233.9 (41.6) [120.0–531.0]	708.8 (26.2) [474.0–1140.0]
T_{max}, h, median (range)	4.0 (3.0–6.0)	6.0 (2.0–12.0)	4.0 (2.0–6.0)
$t_{1/2}$, h, median (range)	36.9 (18.3–59.1)	75.8 (32.6–125.4)	25.0 (17.1–37.8)
CORT118335-P9			
$AUC_{0\text{-}t}$, h*ng/mL, geometric mean (G-CV%) [range]	4,976.4 (43.8) [2,399.1–8,373.1]	4,968.5 (50.2) [2,918.3–11,300.2]	1,508.2 (81.1) [558.6–4,877.9]
$AUC_{0\text{-}inf}$, h*ng/mL, geometric mean (G-CV%) [range]	5,717.3 (52.8) [2,508.9–10,650.0]	9,452.8 (114.7) [3,463.3–65,555.1]	1,614.1 (77.5) [652.8–5,161.5]
C_{max}, ng/mL, geometric mean (G-CV%) [range]	111.0 (28.4) [76.2–190.0]	58.7 (42.5) [41.9–164.0]	93.9 (42.9) [49.5–149.0]
T_{max}, h, median (range)	6.0 (2.0-6.0)	10.0 (4.0-24.0)	4.0 (3.0-6.0)

AUC, area under the curve; C_{max}, maximum concentration; G-CV, geometric coefficient of variation; $t_{1/2}$, elimination half-life; T_{max}, time to maximum concentration.

Plasma Concentration-Time Pharmacokinetic Profiles

Figure 3. Miricorilant Plasma Geometric Mean Concentration Over Time by Hepatic Function

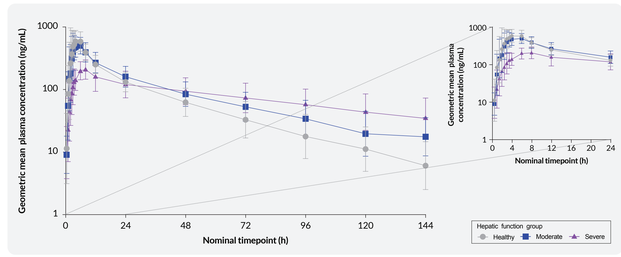
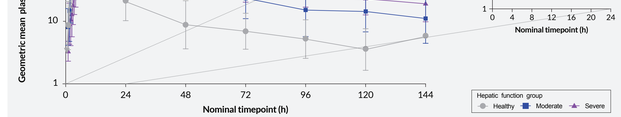


Figure 4. CORT118335-P9 Plasma Geometric Mean Concentration Over Time by Hepatic Function



Statistical Analysis

- Moderate and severe hepatic impairment had minimal impact on the systemic plasma AUC of miricorilant (**Table 7**)
  - Mean miricorilant systemic plasma C_{max} was approximately 67% lower in individuals with severe hepatic impairment versus matched-control healthy volunteers

Table 7. Systemic Plasma Exposure for a Single Dose of Miricorilant in Individuals With Moderate or Severe Hepatic Impairment Compared With Healthy Matched Volunteers

	Geometric LSM ratio (90% geometric CI)[a,b]
Child-Pugh class B	
$AUC_{0\text{-}t}$, h*ng/mL	120.86 (89.36, 163.45)
$AUC_{0\text{-}inf}$, h*ng/mL	126.69 (92.79, 172.97)
C_{max}, ng/mL	82.43 (65.46, 103.80)
Child-Pugh class C	
$AUC_{0\text{-}t}$, h*ng/mL	104.93 (74.30, 148.20)
$AUC_{0\text{-}inf}$, h*ng/mL	141.50 (96.63, 207.21)
C_{max}, ng/mL	33.00 (25.42, 42.82)

[a]Calculated using LSM according to the formula: exp (DIFFERENCE) * 100.
[b]90% geometric CI calculated according to the formula: exp (DIFFERENCE ± t(dfResidual)* SEDIFFERENCE) * 100.
CI, confidence interval; LSM, least-squares means.

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Presenter Disclosures

- Dr. Joseph M. Custodio is employed by and owns stock in Corcept Therapeutics Incorporated