Pharmacokinetics of the Selective Glucocorticoid Receptor Modulator Miricorilant in Healthy Volunteers and Patients with Presumed Metabolic Dysfunction-Associated Steatohepatitis (MASH)

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Summary & Conclusions

- The presented studies characterize the PK/ADME of miricorilant
  - Administration of [^{14}C]-miricorilant to mice resulted in high concentrations of radioactivity in the liver
  - The primary route of miricorilant elimination is hepatic
  - Miricorilant systemic concentrations increased with repeated daily dosing, with accumulation ratios of 1.42 for C_{max} and 1.92 for $AUC_{(0\text{-}24)}$ and steady state exposures achieved by Day 7
  - Miricorilant is a strong inhibitor of CYP2C8 in vivo
  - Miricorilant is a moderate inhibitor of BCRP in vivo
  - Miricorilant does not affect the activity of UGT1A1, CYP3A4, or CYP2C9 in vivo
  - Miricorilant is a moderately sensitive substrate of CYP2C19 in vivo
  - In patients with presumed MASH, miricorilant plasma PK behaved in an approximately dose proportional manner
- Miricorilant was well tolerated in patients and healthy volunteers
- A phase 2b study (MONARCH, NCT06108219) of miricorilant in patients with MASH is currently enrolling

$AUC_{(0\text{-}24)}$, area under the curve from time 0 to 24 hours; ^{14}C, carbon-14; ADME, absorption, distribution, metabolism, and excretion; BCRP, breast cancer resistance protein; C_{max}, maximum measured concentration; CYP, cytochrome P450; MASH, metabolic dysfunction-associated steatohepatitis; PK, pharmacokinetics; UGT1A1, UDP-glucuronyltransferase 1A1.

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See ClinicalTrials.gov for more details on the currently enrolling MONARCH study.

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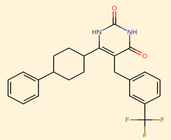
Background

- Miricorilant is an oral, nonsteroidal selective glucocorticoid receptor modulator (SGRM) that acts as a mixed agonist/antagonist of the GR and a modest antagonist of the MR[1]



- Miricorilant is in development for the treatment of MASH
  - Cortisol activity has been associated with the development and progression of MASLD[2]
    - Binding of cortisol to the GR can cause increased availability of energy substrates (such as FFAs) for daytime activities and stress responses
    - By increasing FFA uptake and de novo lipogenesis, cortisol can contribute to excess FFAs in the liver
  - In preclinical models of MASLD and MASH, miricorilant reversed and prevented liver steatosis by preventing lipid accumulation in the liver, and also reduced inflammation and fibrosis stage[3]
  - In a phase 1b study of patients with presumed MASH, miricorilant 100 mg twice weekly was safe, well tolerated, reduced liver fat content, and improved hepatic, glycemic, and lipid markers[4]
- Over 450 patients and healthy volunteers have received miricorilant in clinical trials to date

FFA, free fatty acid; GR, glucocorticoid receptor; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MR, mineralocorticoid receptor.

1 Methods

- In vivo tissue distribution study
  - Tissue distribution of oral [^{14}C]-miricorilant 50 mg/kg was assessed in male albino mice (n=7; timepoints: 1, 4, 8, 12, 24, 72, and 168 h) and in partially pigmented mice (n=4; timepoints: 1, 24, 72, and 168 h)
- ADME study (NCT03878264)
  - Phase 1 study evaluating absorption, distribution, metabolism, and excretion and mass balance recovery of a single oral dose of [^{14}C]-miricorilant 150 mg (administered fed) in male healthy volunteers (30—65 years; BMI 18—30 kg/m^2)
  - PK and safety were assessed
- First-in-human study (NCT03315338)
  - Phase 1, double-blind, randomized, placebo-controlled study in healthy volunteers (18—60 years; BMI 18—30 kg/m^2)
    - Multiple ascending doses cohort: tested 150—900 mg of oral miricorilant (administered fasted) for 14 days
    - Food effect cohort: tested 900 mg of oral miricorilant administered fasted; a minimum of 7 days later, 900 mg of oral miricorilant was administered after a high-fat breakfast
  - PK and safety were assessed
- DDI studies
  - Phase 1, open-label study evaluating the potential effect of miricorilant (400 mg QD orally on Days 4—12) on the PK of different probes (administered fed) in healthy volunteers (18—60 years; BMI 19—32 kg/m^2) (ISRCTN10379288)
    - The following probes were given orally as single doses on Days 1 and 10:
      - repaglinide (0.5 mg), substrate of CYP2C8
      - rosuvastatin (10 mg), substrate of BCRP
      - tolbutamide (500 mg), substrate of CYP2C9
      - midazolam (2.5 mg), substrate of CYP3A4
      - dolutegravir (50 mg), substrate of UGT1A1
  - Phase 1, open-label study evaluating the PK of miricorilant (600 mg orally on Days 1 and 10) in the presence or absence of the strong CYP2C19 inhibitor fluvoxamine (50 mg QD orally on Days 4—12) in healthy volunteers (18—60 years; BMI 19—32 kg/m^2) (NCT05712265)
  - PK and safety were assessed in both studies
- MASH phase 1b study (NCT05117489)
  - Phase 1b, open-label study of adults with presumed MASH
  - Included 11 cohorts of patients who received miricorilant doses ranging from 30—200 mg intermittently or daily for 12 or 24 weeks
  - Efficacy, safety, and PK were assessed
    - PK was assessed under fed conditions

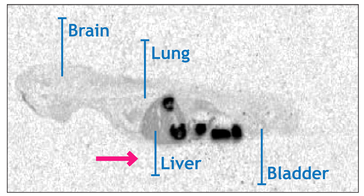
^{14}C, carbon-14; ADME, absorption, distribution, metabolism, and excretion; BCRP, breast cancer resistance protein; BMI, body mass index; CYP, cytochrome P450; DDI, drug-drug interaction; PK, pharmacokinetics; QD, every day; UGT1A1, UDP-glucuronyltransferase 1A1.

Disclosures

JMC, JK, KJ, HJH: employee of and owns stock in Corcept Therapeutics. **KD**: employee of Jade Consultants (Cambridge) Ltd, which provides consultancy services to Corcept Therapeutics. **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 Theratechnologie; consultant for AbbVie/Allergan, Echosens, Fibronostics, Gilead, Intercept, Madrigal, Novo Nordisk, Perspectum, Pfizer, and Zydus.

2 In Vivo Study

Radioactivity in an albino mouse post dose administration of [^{14}C]-miricorilant



- High levels of radioactivity were present in the liver through 8 h post dose administration of [^{14}C]-miricorilant in albino mice
- In pigmented mice, radioactivity was not present at quantifiable levels in melanin-containing tissues (skin and uveal tract)

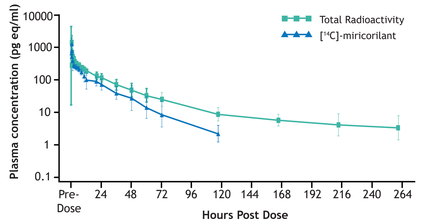
3 Safety

- Overall, miricorilant was safe and well tolerated in patients with MASH and in healthy volunteers, with most TEAEs being mild (grade ≤2)
- Safety results in the phase 1b study of patients with MASH have been previously presented[4]
- Across the presented studies, 205 healthy volunteers received miricorilant
  - No serious TEAEs related to miricorilant were reported in healthy volunteers
  - No significant safety signals were identified

TEAE, treatment-emergent adverse event.

4 ADME Study

Plasma concentrations of [^{14}C]-miricorilant and total radioactivity

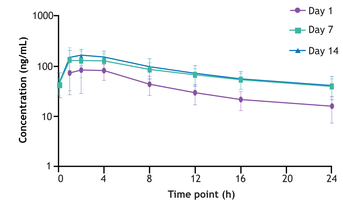


- Following administration of a single oral dose of [^{14}C]-miricorilant 150 mg to healthy volunteers (n=6), 89.1% of the total radioactivity was recovered in the feces, with minimal recovery in the urine (<5%), suggesting that the predominant route of elimination is hepatic
- Parent miricorilant accounted for 57.7% of circulating plasma total radioactivity based on $AUC_{(0\text{-}inf)}$ (ratio of 0.577), indicating that parent was the main circulating species in the plasma following oral administration

$AUC_{(0\text{-}inf)}$, area under the curve from time 0 extrapolated to infinity. Error bars: standard deviation.

5 First-In-Human Study

Time to steady state following miricorilant 150 mg



Geometric mean (geometric CV%)	Miricorilant 150 mg Day 1 n=8	Day 7 n=8	Day 14 n=8
C_{max} (ng/mL)	100 (38.2)	142 (63.5)	169 (30.1)
$AUC_{(0\text{-}24)}$ (ng·h/mL)	896 (38.3)	1730 (44.7)	1940 (39.2)

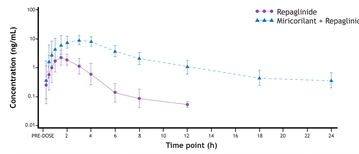
- Systemic concentrations increased with repeated dosing of miricorilant 150 mg daily for 14 days in healthy volunteers (n=8)
- Steady state plasma exposures were achieved by Day 7, resulting in overall accumulation ratios from Days 1 to 7 of 1.42 for C_{max} and 1.92 for $AUC_{(0\text{-}24)}$. Accumulation ratios for Days 1 to 14 were 1.68 for C_{max} and 2.17 for $AUC_{(0\text{-}24)}$, with an elimination half-life of 21.6 h
- Following miricorilant dosing at 100, 300 and 900 mg, exposure increased in a close to dose-proportional manner based on C_{max}, $AUC_{(0\text{-}last)}$, and $AUC_{(0\text{-}inf)}$
- Miricorilant plasma exposures were approximately 3-fold higher following administration of miricorilant 900 mg under fed vs fasted conditions ($AUC_{(0\text{-}last)}$: 25,200 ng·h/mL vs 7,640 ng·h/mL)

$AUC_{(0\text{-}24)}$, area under the curve from time 0 to 24 hours; $AUC_{(0\text{-}last)}$, area under the curve from time 0 to the time of last measurable concentration; C_{max}, maximum measured concentration; CV%, coefficient of variation. Error bars: standard deviation.

6 DDI Studies

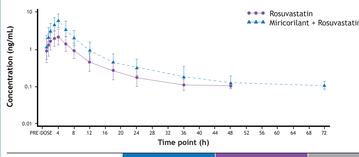
DDI Perpetrator Study

Plasma concentrations of repaglinide ± miricorilant



	Miricorilant + repaglinide GM (G-CV%)	Repaglinide alone GM (G-CV%)	GMR[a] (90% CI)
C_{max} (ng/mL)	10.8 (27.4)	2.94 (62.0)	367 (316—426)
$AUC_{(0\text{-}last)}$ (ng·h/mL)	57.4 (34.6)	6.68 (46.8)	860 (786—941)
$AUC_{(0\text{-}inf)}$ (ng·h/mL)	60.8 (36.5)	7.27 (45.1)	785 (719—857)
$T_{1/2}$ (h)	5.58 (31.9)	1.48 (63.2)	NA

Plasma concentrations of rosuvastatin ± miricorilant



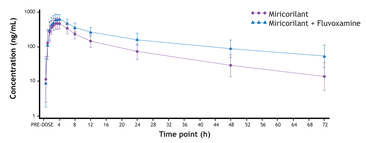
	Miricorilant + rosuvastatin GM (G-CV%)	Rosuvastatin alone GM (G-CV%)	GMR[a] (90% CI)
C_{max} (ng/mL)	6.23 (42.9)	2.35 (49.9)	265 (238—295)
$AUC_{(0\text{-}last)}$ (ng·h/mL)	42.3 (43.1)	17.1 (51.7)	247 (228—269)
$AUC_{(0\text{-}inf)}$ (ng·h/mL)	47.6 (44.6)	20.7 (45.8)	236 (217—256)
$T_{1/2}$ (h)	11.6 (86.1)	6.81 (63.8)	NA

- 30 healthy volunteers were enrolled and completed the study
- Repaglinide C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ were increased by approximately 4-fold, 9-fold and 8-fold in the presence of miricorilant 400 mg vs repaglinide dosed alone, indicating that miricorilant is an inhibitor of CYP2C8
- Rosuvastatin C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ were all increased by approximately 2.5-fold in the presence of miricorilant 400 mg vs rosuvastatin dosed alone, indicating that miricorilant moderately inhibited BCRP
- Miricorilant 400 mg did not have a clinically meaningful effect on UGT1A1, CYP3A4, or CYP2C9

CI, confidence interval; DDI, drug-drug interaction; G-CV%, geometric coefficient of variation; GM, geometric mean; GMR, adjusted geometric mean ratio; $T_{1/2}$, half life. [a]GMRs expressed as percentages. Error bars: standard deviation.

DDI Victim Study

Plasma concentrations of miricorilant ± fluvoxamine



	Miricorilant + fluvoxamine GM (G-CV%)	Miricorilant alone GM (G-CV%)	GMR[a] (90% CI)
C_{max} (ng/mL)	643 (33.2)	492 (37.3)	131 (121—141)
$AUC_{(0\text{-}last)}$ (ng·h/mL)	11,700 (39.8)	6,140 (44.8)	190 (173—209)
$AUC_{(0\text{-}inf)}$ (ng·h/mL)	14,600 (52.8)	6,700 (48.6)	218 (196—242)
$T_{1/2}$ (h)	31.4 (41.3)	20.6 (35.1)	NA

- Following coadministration of miricorilant 600 mg and fluvoxamine 50 mg, miricorilant C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ were increased by 1.3-, 1.9- and 2.2-fold, respectively, as compared with miricorilant administered alone, indicating that miricorilant is a moderately sensitive substrate of CYP2C19

[a]GMRs expressed as percentages. Error bars: standard deviation.

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(1) Hunt HJ et al. *Bioorg Med Chem Lett*. 2012;22(24):7376-7380.
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(3) Koorneef LL et al. *Endocrinology*. 2018; 159(12):3925-3936.
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7 Continuous Daily Miricorilant Dosing in a Phase 1b Study of Patients With Presumed MASH

- Miricorilant plasma PK behaved in an approximately dose-proportional manner across the range of miricorilant doses and dosing regimens evaluated in patients with presumed MASH (n=71)

Steady state PK in patients receiving daily miricorilant 100 mg[a]

Once-daily dose (100 mg)	C_{max} (ng/mL) n=18	$AUC_{0\text{-}24}$ (ng·h/mL) n=13
Geometric mean (geometric CV%) [median (range)]	170 (151) [207 (4.4—610)]	4148 (40.8) [4262 (1672—7416)]

[a]All patients who received daily miricorilant 100 mg during the phase 1b PK analysis.

8 Twice-Weekly Miricorilant Dosing in a Phase 1b Study of Patients With Presumed MASH

- The currently enrolling phase 2b MONARCH trial (NCT06108219) includes patients with MASH receiving miricorilant 100 mg twice weekly

PK in patients receiving twice-weekly miricorilant 100 mg[a]

Twice-weekly dose (100 mg)	C_{max} (ng/mL) n=13	$AUC_{0\text{-}24}$ (ng·h/mL) n=11
Geometric mean (geometric CV%) [median (range)]	98.0 (130) [114 (8.1—346)]	1337 (49.7) [1135 (898—4294)]

[a]All patients received twice-weekly miricorilant 100 mg during the phase 1b PK analysis.