Effects of Itraconazole and Carbamazepine on the Pharmacokinetics of Remlifanserin (ACP-204) in Healthy Adults

Poster No. T2

Mona Darwish[1]; Bryan Dirks[1]; Amy Yamamoto[2]; Brian Raether[2]; Sanjeev Pathak[1]

[1]Acadia Pharmaceuticals Inc., Princeton, NJ; [2]Acadia Pharmaceuticals Inc., San Diego, CA **Presenting Author:** Mona Darwish

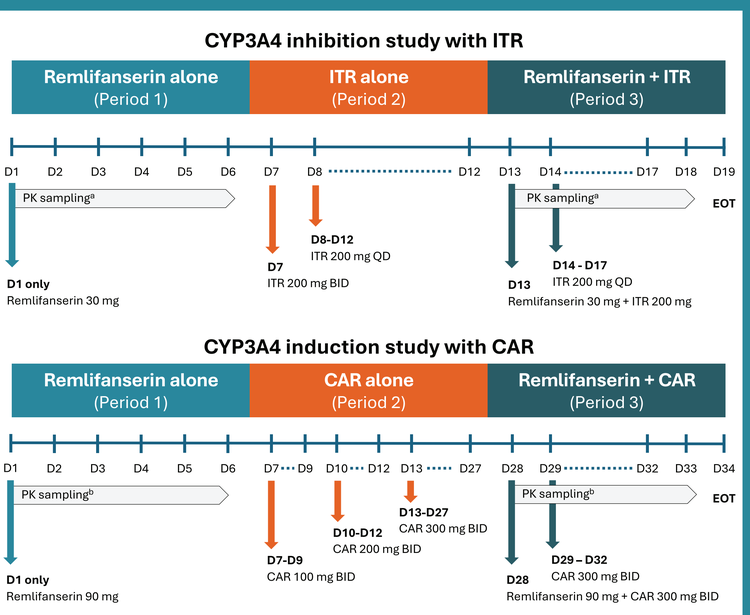
INTRODUCTION

- Remlifanserin (ACP-204) is a selective 5-HT_{2A} receptor inverse agonist in development for the treatment of Alzheimer's disease psychosis and Lewy body dementia psychosis
- In vitro data indicate that remlifanserin is eliminated primarily by hepatic oxidative metabolism via CYP3A4. The primary circulating metabolite, *N*-desmethyl remlifanserin, is also formed and metabolized by CYP3A4
- Herein, we present findings from separate DDI studies aimed at elucidating the effects of the strong CYP3A4 inhibitor, ITR, and the strong CYP3A4 inducer, CAR, on the PK of remlifanserin

METHODS

Study Design

- The PK of a single oral dose of remlifanserin, in the absence or presence of multiple oral doses of ITR or CAR, was assessed in two phase 1, open-label, fixed-sequence, 3-period DDI studies in healthy adults
- In each study, participants were administered study drugs via three treatment cycles: remlifanserin alone (period 1), ITR or CAR alone (period 2), and remlifanserin + ITR or CAR (period 3)



[a]PK samples were collected on day 1 (period 1) and day 13 (period 3) prior to remlifanserin administration and up to 120 h after remlifanserin administration. [b]PK samples were collected on day 1 (period 1) and day 28 (period 3) prior to remlifanserin administration and up to 120 h after remlifanserin administration.

Statistical Methods

- Participants who received ≥1 dose of study drug were included in the safety dataset, and those with sufficient data to calculate ≥1 PK parameter were included in the PK dataset
- All PK parameters of remlifanserin and *N*-desmethyl remlifanserin, including plasma concentrations, were summarized by treatment period using descriptive statistics
- Log-transformed PK parameters (eg, C_{max}, $AUC_{0-\infty}$, and AUC_{0-t}) were analyzed using a mixed-effects model with treatment period as a fixed effect and participant as a random effect. Period 3 was compared to period 1 using GLSM ratios (%) and corresponding 90% CIs
- Safety endpoints (ie, TEAEs, clinically significant findings on physical examination, vital signs, laboratory tests, and ECG parameters) were evaluated across all treatment periods

Abbreviations: $\%AUC_{ext}$, percentage of area under the (plasma) concentration-time curve extrapolated from time t to infinity; 5-HT_{2A}, serotonin 2A; AUC, area under the (plasma) concentration-time curve; $AUC_{0-\infty}$, AUC from time 0 to infinity; AUC_{0-t}, AUC from time 0 to time t; BID, twice daily; CAR, carbamazepeine; CI, confindence interval; CL/F, apparent systemic clearance following nonintravenous administration; C_{max}, maximum observed drug concentration; CYP3A4, cytochrome P450 3A4; D, day; DDI, drug-drug interaction; ECG, electrocardiogram; GLSM, geometric least squares mean; h, hours; ITR, itraconazole; M/P, metabolite to parent; PK, pharmacokinetic; QD, once daily; SD, standard deviation; SE, standard error; $t_{1/2}$, apparent terminal elimination half-life; TEAE, treatment-emergent adverse event; T_{max}, time to maximum observed drug concentration; V_z/F, apparent volume of distribution following nonintravenous administration.

Presented at the American Society of Clinical Psychopharmacology Annual Meeting; May 25-29, 2026; Miami, FL, USA

ACADIA®

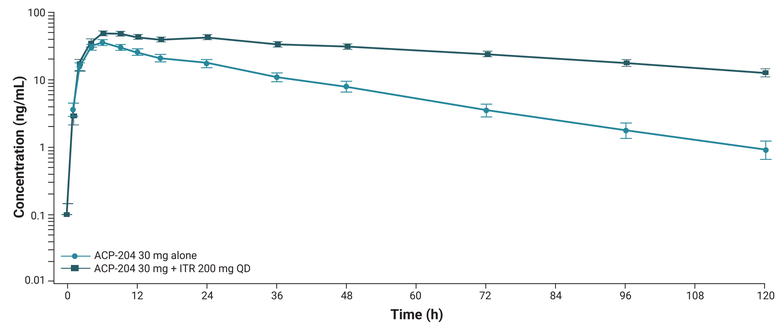
RESULTS

CYP3A4 Inhibition Study With ITR

- Seventeen healthy adult participants were included in the safety dataset and PK dataset

Impact of ITR on remlifanserin PK

Remlifanserin plasma concentrations were markedly higher and cleared more slowly with concomitant treatment with ITR vs remlifanserin alone



PK analysis dataset. Semi-log scales.

PK parameter	Remlifanserin 30 mg alone		Remlifanserin 30 mg + ITR 200 mg QD	
	n	Mean (SD)	n	Mean (SD)
C_{max}, ng/mL	17	37.9 (12.9)	17	51.9 (15.5)
AUC_{0-t}, ng·h/mL	17	1121 (530)	17	3397 (1158)
$AUC_{0-\infty}$, ng·h/mL	17	1159 (578)	9	3581 (1610)
AUC_{ext}, %	17	2.51 (2.62)	9	15.5 (3.41)
T_{max}[a], h	17	6.00 (4.00, 6.01)	17	9.00 (4.00, 12.0)
$t_{1/2}$, h	17	21.3 (5.87)	16	51.4 (11.2)
CL/F, L/h	17	30.6 (11.2)	16	8.13 (3.57)
V_z/F, L	17	888 (265)	16	566 (156)

PK analysis dataset.[a]Median, minimum, and maximum were presented for T_{max} instead.

Upon coadministration with ITR, the C_{max} of remlifanserin increased by 38%, while the extent of exposure increased 3-fold

PK parameter	Treatment period	n	GLSM ratio	90% CI for GLSM ratio
C_{max}	Remlifanserin 30 mg + ITR 200 mg QD	17	138.27	(130.21, 146.83)
	Remlifanserin 30 mg alone	17		
AUC_{0-t}	Remlifanserin 30 mg + ITR 200 mg QD	17	311.93	(275.10, 353.69)
	Remlifanserin 30 mg alone	17		
$AUC_{0-\infty}$[a]	Remlifanserin 30 mg + ITR 200 mg QD	9	335.45	(300.76, 374.15)
	Remlifanserin 30 mg alone	9		

PK analysis dataset. [a]Only participants with $\%AUC_{ext}$ <20% and reliable $AUC_{0-\infty}$ values for both period 1 and period 3 are included in the statistical analysis.

- For *N*-desmethyl-remlifanserin, the presence of ITR reduced the mean M/P ratio for C_{max} and AUC_{0-t} by approximately 30% and 57%, respectively, compared with the administration of remlifanserin alone

Safety and tolerability

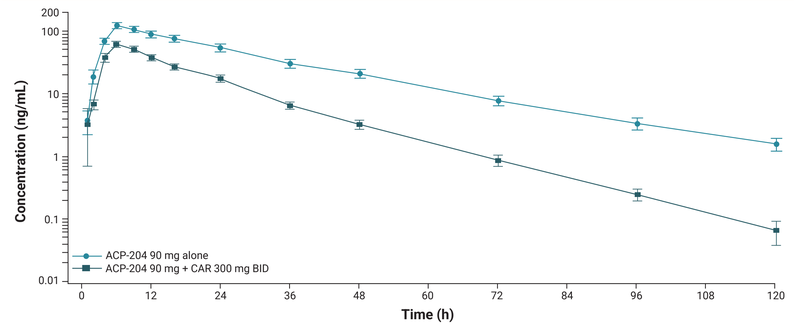
- TEAEs related to remlifanserin alone were reported by 3 participants vs 5 with ITR alone
- Most common TEAEs reported in ≥2 participants in any period were headache (n=4, 23.5%); fatigue, limb discomfort, and nasal congestion (n=2, 11.8% each); all TEAEs were mild
- No serious TEAEs, TEAEs leading to study drug discontinuation or death were reported

CYP3A4 Induction Study With CAR

- Seventeen healthy adult participants were included in the safety dataset, and 16 in the PK dataset

Impact of CAR on remlifanserin PK

Remlifanserin plasma concentrations were substantially lower and cleared more rapidly with concomitant treatment with CAR vs remlifanserin alone



PK analysis dataset. Semi-log scales.

PK parameter	Remlifanserin 90 mg alone		Remlifanserin 90 mg + CAR 300 mg BID	
	n	Mean (SD)	n	Mean (SD)
C_{max}, ng/mL	16	124 (38.7)	16	61.1 (23.1)
AUC_{0-t}, ng·h/mL	16	3154 (1359)	16	1037 (437)
$AUC_{0-\infty}$, ng·h/mL	16	3203 (1402)	16	1041 (438)
AUC_{ext}, %	16	1.33 (0.946)	16	0.401 (0.159)
T_{max}[a], h	16	6.00 (6.00, 9.01)	16	6.00 (4.08, 6.01)
$t_{1/2}$, h	16	19.4 (3.20)	16	13.4 (2.94)
CL/F, L/h	16	32.9 (14.2)	16	98.5 (33.8)
V_z/F, L	16	909 (420)	16	1902 (741)

PK analysis dataset. [a]Median, minimum, and maximum were presented for T_{max} instead.
Note: One participant vomited three times during period 1 between 0.5 and 8 h postdose; therefore, was excluded from the PK dataset.

Upon coadministration with CAR, the C_{max} of remlifanserin was reduced by approximately 50%, while the extent of exposure was reduced to approximately 33%

PK parameter	Treatment period	n	GLSM ratio	90% CI for GLSM ratio
C_{max}	Remlifanserin 90 mg + CAR 300 mg BID	16	48.29	(43.34, 53.81)
	Remlifanserin 90 mg alone	16		
AUC_{0-t}	Remlifanserin 90 mg + CAR 300 mg BID	16	33.16	(29.47, 37.32)
	Remlifanserin 90 mg alone	16		
$AUC_{0-\infty}$[a]	Remlifanserin 90 mg + CAR 300 mg BID	9	32.85	(29.20, 36.96)
	Remlifanserin 90 mg alone	9		

PK analysis dataset. [a]Only participants with $\%AUC_{ext}$ <20% and reliable $AUC_{0-\infty}$ values for both period 3 and period 1 are included in the statistical analysis.

- For *N*-desmethyl-remlifanserin, the presence of CAR increased the mean M/P exposure ratio for both C_{max} and AUC_{0-t} by approximately 2-fold compared with the administration of remlifanserin alone

Safety and tolerability

- TEAEs related to remlifanserin alone were reported in 8 participants vs 13 with CAR alone
- Most common TEAEs reported in ≥2 participants in any period were fatigue and somnolence (n=7, 41.2% each); constipation and headache (n=6, 35.3% each); and insomnia (n=4, 23.5%); most TEAEs were mild
- No serious TEAEs, TEAEs leading to study drug discontinuation or death were reported

CONCLUSIONS

- Coadministration of remlifanserin with strong CYP3A4 inhibitor ITR markedly increased remlifanserin systemic exposure, whereas coadministration with strong CYP3A4 inducer CAR decreased remlifanserin systemic exposure
- No serious TEAEs or clinically meaningful changes in physical examination, vital signs, laboratory tests, or ECG results were observed in either study
- Remlifanserin is currently being evaluated in Phase 2/3 studies in patients with psychotic symptoms associated with Alzheimer's disease and Lewy body dementia. DDIs due to coadministration of remlifanserin with common therapies in these populations, such as donepezil, memantine, rivastigmine, or anti-amyloid antibodies such as lecanemab-irmb (Alzheimer's only), are unlikely, as these agents are not clinically relevant inhibitors or inducers of CYP3A4[1-4]

REFERENCES

1. ARICEPT® (donepezil hydrochloride). Full Prescribing Information. 2018.
2. NAMENDA® (memantine hydrochloride). Full Prescribing Information. 2018.
3. EXELON® (rivastigmine tartrate). Full Prescribing Information. 2018.
4. LEQEMBI® (lecanemab-irmb). Full Prescribing Information. 2025.

ACKNOWLEDGMENTS

This study was funded by Acadia Pharmaceuticals Inc. (San Diego, California). Medical writing support was provided by Citrus Health Group, Inc. (Chicago, Illinois) and was funded by Acadia Pharmaceuticals Inc.

DISCLOSURES

MD, BD, AY, BR, and **SP** are employees of Acadia Pharmaceuticals Inc. and may own stock and/or stock options.

Scan code to view poster