Nonclinical Characterization of ACP-204, a Novel Second-Generation 5-HT$_{2A}$ Inverse Agonist

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INTRODUCTION

- Pimavanserin, a potent and selective 5-HT$_{2A}$ inverse agonist/antagonist, is US Food and Drug Administration–approved for hallucinations and delusions associated with Parkinson's disease psychosis[1,2]
- The long half-life of pimavanserin ($t_{1/2}$ ≈ 57 h) increases the time needed to achieve steady-state therapeutic levels[2]
- In addition, pimavanserin prolongs the cardiac QT interval, which limits the dose that can be administered and restricts its use to patients without known QT prolongation or who are not concurrently treated with other drugs that have this effect[2]
- Here, we describe the pharmacologic and pharmacokinetic (PK) properties and nonclinical safety assessments of a novel 5-HT$_{2A}$ inverse agonist, ACP-204, that has a similar pharmacological profile to pimavanserin with a shorter half-life and lower risk of QT prolongation

METHODS

- The IC_{50} and K_b or K_i of ACP-204 vs pimavanserin for 5-HT$_{2A}$ and 5-HT$_{2C}$ receptor binding were determined using cell-based RSAT functional assays[1] and PI hydrolysis and radioligand binding assays
- The effects of various concentrations of ACP-204 on electrical currents in HEK-293 cells stably expressing recombinant hERG[3] or recombinant human $Na_V1.5$ sodium channels,[4] or in CHO cells stably over-expressing human $Ca_V1.2$ L-type calcium channels,[5] were assessed with manual patch clamp assays at Charles River Laboratories (Cleveland, OH) according to the Charles River protocols
- The effect of ACP-204 on head twitches induced by DOI, a 5-HT$_{2A/2C}$ agonist,[6] was assessed in male C57BL/6 mice and male Sprague-Dawley rats
  - DOI (2.5 mg/kg) was administered IP 60 minutes following SC (mice and rats) or 165 minutes following PO (rats) administration of the indicated doses of ACP-204 or vehicle (0.9% saline)
  - Head twitching was defined as rapid, bidirectional, rotational head movements (ie, wet dog shakes) unrelated to normal exploratory or grooming behaviors
- The ability of various doses of ACP-204 to reduce hyperlocomotion induced by MK-801[7] (dizocilpine; 0.4 mg/kg, IP) was evaluated in male BALB/c mice and compared with the reference 5-HT$_{2A}$ antagonist M100907[8] (0.3 mg/kg) or vehicle
  - Locomotor activity was measured by an automated infrared photobeam monitoring apparatus (Kinder Scientific) during a 90-minute activity cycle
- PET was performed in a male Rhesus monkey (16 kg, 12 years old) using [^{18}F]altanserin, a radioligand for the 5-HT$_{2A}$ receptor,[9] to determine the effect of ACP 204 on 5-HT$_{2A}$ receptor occupancy
  - Images were acquired over a 120-minute period and processed using PMOD v 3.802 (PMOD Technologies)
  - The outcome measure was BP_{ND} using the cerebellum as the nondisplaceable reference region
  - 5-HT$_{2A}$ receptor occupancy was calculated using the following formula:
    [1 - (post-ACP-204 BP_{ND} / Baseline BP_{ND})] × 100
  - 5-HT$_{2A}$ receptor occupancy and ACP-204 plasma concentration were fit with a single-binding site model with Hill slope = 1
- PK parameters of ACP-204 were determined using noncompartmental analysis (Phoenix WinNonlin™ software v 6.3) of the plasma concentration of ACP-204 over time in male (230–260 g) and female (200–230 g) Sprague-Dawley rats. These parameters were also determined from the concentration of ACP-204 over time in plasma and CSF in male Cynomolgus monkeys (2–5 kg, ≥2 years old)
- Repeat-dose (chronic) oral toxicity studies of up to 6 months in Sprague-Dawley rats and up to 9 months in Cynomolgus monkeys were performed
- Safety margins were estimated by comparing drug exposure at the maximum effective doses for DOI-induced head twitches in rats with the NOAELs in the toxicity studies

RESULTS

- At 5-HT$_{2A}$, ACP-204 acted as an antagonist/inverse agonist and had potencies of 0.3–0.5 nM, which were 3- to 9-fold more potent than pimavanserin (**Table 1**)
- At 5-HT$_{2C}$, ACP-204 acted as an antagonist/inverse agonist and exhibited potencies of 16–37 nM, which were up to 2.7× more potent than pimavanserin

Table 1. Comparison of the Functional Profiles of ACP-204 and Pimavanserin at 5-HT$_{2A}$ and 5 HT$_{2C}$ Receptors[a]

	RSAT assay						PI assay		
	Inverse Agonism			Antagonism[b]			Antagonism		
Drug	IC_{50} (nM)	Range (nM)	n	K_b (nM)	Range (nM)	n	K_b (nM)	Range (nM)	n
5-HT$_{2A}$									
ACP-204	0.3	0.1–0.5	9	0.3	0.1–0.7	9	0.5	0.3–0.9	3
Pimavanserin	2.7	1.7–4.6	22	1.9	0.9–4.1	11	1.7	1.0–2.9	3
5-HT$_{2C}$									
ACP-204	37	32–43	6	17	10–29	9	16	14–18	2
Pimavanserin	100	72–138	9	41	23–72	12	14	9–18	3

5-HT$_{2A}$, 5-hydroxytryptamine receptor 2A; 5-HT$_{2C}$, 5-hydroxytryptamine receptor 2C; IC_{50}, drug concentration needed for 50% inhibition; K_b, inhibition constant of a functional antagonist; PI, phosphatidylinositol hydrolysis assay; RSAT, Receptor Selection and Amplification Technology. Data are expressed as means ± standard deviations shown as ranges.
[a]The "INI" (nonedited) and "VGV" (fully edited) isoforms of human 5-HT$_{2C}$ were used in inverse agonist assays and functional antagonist assays, respectively.
[b]The K_b value was calculated from the IC_{50} value by the method of Cheng and Prusoff.[10]

ABBREVIATIONS

BP_{ND}, binding potential; CHO, Chinese hamster ovary; Cl, systemic clearance; CSF, cerebrospinal fluid; DOI, 2,5-dimethoxy-4-iodoamphetamine; hERG, human ether-à-go-go-related gene; IC_{50}, half-maximal inhibitory concentration; IP, intraperitoneal; IV, intravenous; K_b or K_i, equilibrium dissociation constant; NOAEL, no-observed-adverse-effect level; PET, positron emission tomography; PI, phosphatidylinositol; PO, oral; RSAT, Receptor Selection and Amplification Technology; SC, subcutaneous; $t_{1/2}$, apparent terminal elimination half-life; V_{ss}, apparent volume of distribution at steady-state

- Radioligand binding assays showed that the binding affinity of ACP-204 for 5-HT$_{2A}$ and 5-HT$_{2B}$ receptors was similar to that of pimavanserin (K_i = 0.14 vs 0.11 nM for 5-HT$_{2A}$, respectively; and 372 vs 513 nM for 5-HT$_{2B}$, respectively), but weaker at 5-HT$_{2C}$ receptors (K_i = 1.86 vs 0.51 nM, respectively; **Table 2**)

Table 2. Radioligand Binding Activity of ACP-204 and Pimavanserin at 5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$ Receptors Expressed in CHO-K1 Cells

	5-HT$_{2A}$			5-HT$_{2B}$			5-HT$_{2C}$		
Drug	Mean K_i (nM)	SD	n	Mean K_i (nM)	SD	n	Mean K_i (nM)	SD	n
ACP-204	0.14	0.0	2	372	ND	1	1.86	ND	1
Pimavanserin	0.11	0.1	2	513	0.3	2	0.51	0.1	2

CHO, Chinese hamster ovary; K_i, inhibition constant; ND, not determined. Data are shown as mean ± standard deviation.

- ACP-204 did not have any appreciable functional activity ("off-target" effects) against 19 other monoamine targets and at 5 µM had no relevant interaction (ie, <50% inhibition) against 56 additional targets as assessed by radioligand binding (data not shown)
- ACP-204 reduced the potential to impact ion channels important in cardiovascular function compared with pimavanserin. ACP-204 inhibited hERG, $Ca_V1.2$ L-type calcium channel, and $Na_V1.5$ sodium channel currents with half-maximal inhibitory concentration (IC_{50}) values of 1.8, 3.5, and >10 µM, respectively, compared with 0.2, 1.2, and 1.2 µM for pimavanserin (**Table 3**)

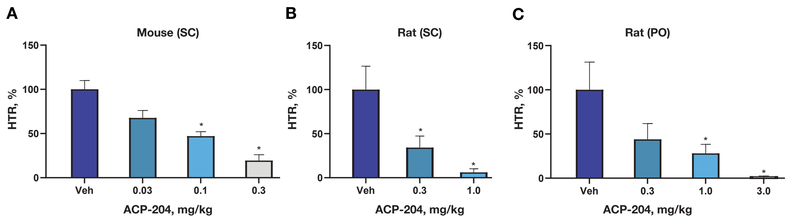
Table 3. Inhibition of Cardiac Ion Channel Currents by ACP-204 vs Pimavanserin as Assessed by In Vitro Patch Clamp Assays

	IC_{50} (µM)		
Drug	hERG	$Ca_V1.2$	$Na_V1.5$
ACP-204	1.8	3.5	>10[a]
Pimavanserin	0.2	1.2	1.2

$Ca_V1.2$, $Ca_V1.2$ L-type calcium channel; hERG, human ether-à-go-go-related gene; IC_{50}, half-maximal inhibitory concentration; $Na_V1.5$, $Na_V1.5$ sodium channel.
[a]43% inhibition at 10 µM.

- ACP-204 potently suppressed DOI-induced head twitches in mice and rats with minimum effective SC doses of 0.1 and 0.3 mg/kg, respectively; it achieved nearly complete suppression in mice and rats at SC doses of 0.3 and 1 mg/kg, respectively, and at an oral dose of 3 mg/kg in rats (**Figure 1**)

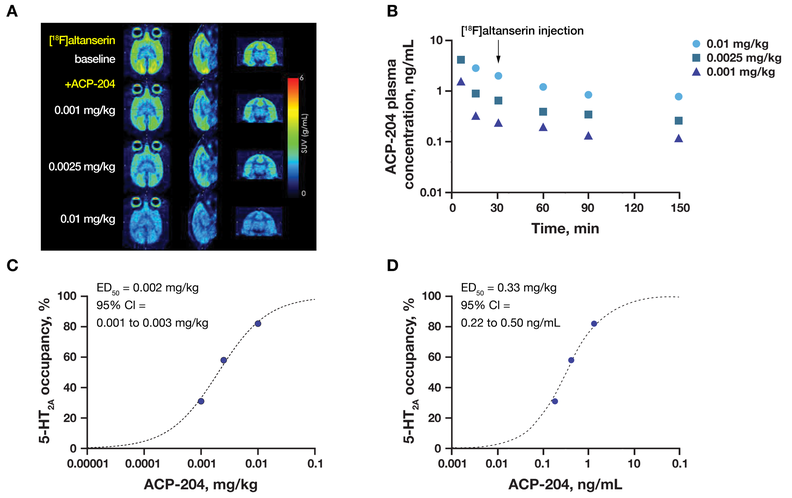
Figure 1. Inhibition of DOI-Induced Head-Twitch Response by ACP-204 vs Vehicle in Mice and Rats



ANOVA, analysis of variance; HTR, head-twitch response; PO, oral; SC, subcutaneous; SEM, standard error of the mean; Veh, vehicle.
HTR, % = (number of head twitches in animals treated with ACP-204) / (number of head twitches in animals treated with vehicle) × 100. In panels A, B, and C, 100% HTR corresponds to 28.3, 16.6, and 19.6 head twitches, respectively.
In panel A, each treatment group had 6 male C57BL/6 mice. In panels B and C, each treatment group had 6 and 8 male Sprague-Dawley rats, respectively.
Data are depicted as mean ± SEM. *P<0.05 vs vehicle using ordinary one-way ANOVA with Dunnett's multiple comparisons test.

- ACP-204 suppressed MK-801–induced locomotor activity in mice with a minimum effective dose of 0.1 mg/kg and with comparable efficacy to M100907 (data not shown)
- PET studies in a Rhesus monkey demonstrated that a 0.002 mg/kg dose of ACP-204 blocked 50% of [^{18}F]altanserin binding to central 5-HT$_{2A}$ receptors (**Figure 2**)
- The plasma concentration that corresponded to 50% blockade of [^{18}F]altanserin binding was 0.33 ng/mL

Figure 2. PET Imaging and Determination of the Occupancy of Central 5-HT$_{2A}$ Receptors by ACP-204 in a Rhesus Monkey.



CI, confidence interval; EC_{50}, ACP-204 plasma concentration that blocked 50% of [^{18}F]altanserin binding; ED_{50}, ACP-204 dose that blocked 50% of [^{18}F]altanserin binding; PET, positron emission tomography; SUV, standardized uptake value.
(A) PET images of the standardized uptake of [^{18}F]altanserin averaged over 0–120 minutes in the brain of a Rhesus monkey. **(B)** Plasma concentrations of ACP-204 over time. **(C)** Nonlinear regression curve of 5-HT$_{2A}$ occupancy vs nominal dose levels of ACP-204. **(D)** Nonlinear regression curve of 5-HT$_{2A}$ occupancy vs plasma concentration of ACP-204; drug concentrations were averaged over 30–150 minutes.

- In Sprague-Dawley rats, ACP-204 had high oral bioavailability, moderate Cl, and a V_{ss} considerably higher than total body water (**Table 4**)

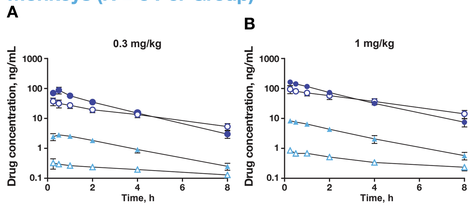
Table 4. Pharmacokinetics of ACP-204 in Sprague-Dawley Rats (N = 3 Per Group)

Parameter	Male rat 1 mg/kg IV	Female rat 1 mg/kg IV	Male rat 10 mg/kg PO	Female rat 10 mg/kg PO
$AUC_{0-\infty}$ (h × ng/mL)	301	390	1090	4975
Cl (mL/min/kg)	42.7	33.1	NA	NA
V_{ss} (L/kg)	7.85	6.24	NA	NA
$t_{1/2}$ (h)	2.27	1.95	2.95	5.22
t_{max} (h)	NA	NA	3.33	3.33
C_{max} (ng/mL)	NA	NA	138	432
F (%)	NA	NA	36	98

$AUC_{0-\infty}$, area under the concentration-time curve from the first sampled data point and extrapolated to infinity; Cl, systemic clearance following intravenous administration; C_{max}, maximum concentration following intravenous administration; F, fraction of the active form of a drug that reaches system circulation unaltered; IV, intravenous; NA, not applicable; PO, oral; $t_{1/2}$, apparent terminal elimination half-life; t_{max}, time to maximum concentration following intravenous administration; V_{ss}, apparent volume of distribution at steady-state following intravenous administration.

- In male Cynomolgous monkey, total drug exposure and Cl was similar, but V_{ss} and $t_{1/2}$ were approximately 2-fold higher for pimavanserin than for ACP-204, and drug exposure in CSF was approximately 5-fold higher for ACP-204 than pimavanserin (**Table 5** and **Figure 3**)
- Using these PK data for ACP-204, the clinical $t_{1/2}$ of ACP-204 was estimated to be 14.7–21.7 h, substantially shorter than pimavanserin ($t_{1/2}$ ≈ 57 h)[2]

Figure 3. Kinetics and Uptake of ACP-204 and Pimavanserin in the Brain of Cynomolgus Monkeys (N = 3 Per Group)



CSF, cerebrospinal fluid.
ACP-204 and pimavanserin were administered as intravenous bolus doses of **(A)** 0.3 mg/kg or **(B)** 1.0 mg/kg, and then drug concentrations in plasma and CSF were determined at the indicated time points.

Table 5. Pharmacokinetics of ACP-204 and Pimavanserin in Cynomolgus Monkeys[a]

Parameter, mean (SD)	ACP-204	Pimavanserin
$t_{1/2}$ (h)	3.0 (0.3)	4.5 (0.4)
V_{ss} (L/kg)	5.8 (1.7)	11.2 (2.3)
Cl (mL/min/kg)	29.9 (8.4)	33.8 (6.9)
CSF C_{max}/plasma C_{max} (%)	4.1 (1.2)	0.9 (0.1)
CSF $AUC_{0\text{-last}}$/plasma $AUC_{0\text{-last}}$ (%)	4.9 (0.6)	0.7 (0.1)

$AUC_{0\text{-last}}$, area under the concentration-time curve from the first observed concentration to the last measurable concentration; Cl, systemic clearance following intravenous administration; C_{max}, maximum concentration following intravenous administration; CSF, cerebrospinal fluid; $t_{1/2}$, apparent terminal elimination half-life; V_{ss}, apparent volume of distribution at steady-state following intravenous administration.
[a]Data are mean (SD) from 3 independent experiments with 0.3, 1, or 2 mg/kg intravenous bolus doses. Each experiment evaluated 3 animals per drug.

- ACP-204 was generally well tolerated in the chronic oral monkey and rat toxicity studies, with NOAELs the top doses tested (40 mg/kg/day for monkeys, 60 mg/kg/day for male rats, and 40 mg/kg/day for female rats)
  - Safety margins based on these toxicity studies were estimated to be 30- to 47-fold when compared to preclinical assessment of maximum effective doses
  - No evidence of phospholipidosis, a finding observed in animal species with pimavanserin, was observed in ACP-204 chronic toxicity studies in rats and monkeys
  - No QTc findings were observed when assessed in the chronic monkey study

CONCLUSIONS

- Compared with pimavanserin, ACP-204 is more potent at 5-HT$_{2A}$ receptors, with significantly lower potency at hERG and other cardiac ion channels associated with QT prolongation
- PET studies revealed that ACP-204 potently occupies central 5-HT$_{2A}$ receptors in Rhesus monkeys
- PK studies showed that substantially more free ACP-204 enters the central nervous system compared with pimavanserin and predict that once-daily dosing of ACP-204 is feasible given the shorter $t_{1/2}$
- Nonclinical safety studies demonstrated that ACP-204 has ample safety margins to support evaluation in ongoing clinical studies

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DISCLOSURES
ESB, **PMD**, and **SP** are employees of Acadia Pharmaceuticals and may own stock and/or stock options.

KEY CONTRIBUTORS
All authors contributed to the conceptualization, design, analysis, and interpretation of this work, as well as the ctritical review of the abstract and poster.

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