An Open-Label Study to Investigate the 5-HT$_{2A}$ Receptor Occupancy of ACP-204 With the PET Ligand [^{18}F]Altanserin in Healthy Adult Males

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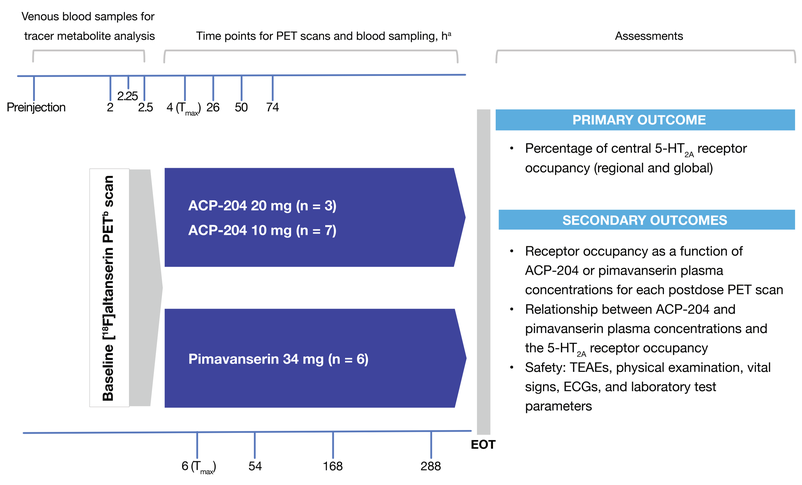
INTRODUCTION

- The selective serotonin 2A (5-HT$_{2A}$) inverse agonist pimavanserin is the only US Food and Drug Administration–approved therapy for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP)[1]
- However, treatment with pimavanserin incurs the potential risk of QT prolongation[1]
- ACP-204 is a potent and selective antagonist and inverse agonist of 5-HT$_{2A}$ receptors with no appreciable interactions at any other targets, including dopaminergic, histaminergic, adrenergic, muscarinic, or other serotonergic receptor subtypes
- ACP-204 has a low potential for engagement with ion channels, such as hERG, that are associated with long QT syndromes;[2] it may, therefore, be less likely than pimavanserin to increase QT intervals at higher doses
- ACP-204 has been tested and is well tolerated in single doses up to 180 mg in healthy adults and multiple doses up to 60 mg and 130 mg in healthy elderly and adult patients, respectively, with no observed QT prolongation and a substantially shorter half-life compared with pimavanserin (~21 h vs ~57 h, respectively)
- This study compared the 5-HT$_{2A}$ receptor occupancy of ACP-204 with that of pimavanserin using fluorine-18 [^{18}F]altanserin, a radiopharmaceutical with high specificity and selectivity to 5-HT$_{2A}$ receptors
- The findings of this study were used to inform the selection of target doses for ongoing clinical trials evaluating the efficacy of ACP-204 in Alzheimer's disease psychosis

METHODS

- This phase 1, open-label, single-center study enrolled healthy adult males aged 18 to 55 years with a body mass index between 18 and 32 kg/m^2 (**Figure 1**)
  - Venous blood samples for tracer metabolite analysis were collected at preinjection of [^{18}F]altanserin and at approximately 2.0, 2.25, and 2.5 hours after initiating the [^{18}F]altanserin infusion
  - Predose (baseline) [^{18}F]altanserin positron emission tomography (PET) scans were performed between 2 weeks and 2 days prior to the treatment period
  - Patients were given a single oral dose of either ACP-204 or pimavanserin in a fasted state and completed 2 postdose [^{18}F]altanserin PET scans and blood samplings at various time points after administration
  - Patients were discharged after completion of all samplings and returned 2 ±1 day(s) later for end-of-treatment assessments (EOTs), followed by safety assessments 7 (±2) days after EOTs

Figure 1. Study design



ECG, electrocardiogram; EOT, end of treatment; PET, positron emission tomography; TEAE, treatment-emergent adverse event; T_{max}, time to maximum plasma concentration; $t_{1/2}$, half-life; 5-HT$_{2A}$, 5-hydroxytryptamine (serotonin) receptor subtype 2A.
[a]Sampling time points were selected based on the T_{max} and $t_{1/2}$ of each drug and aimed to cover a period of 5 consecutive half-lives.
[b]During all PET imaging sessions, [^{18}F]altanserin was administered intravenously over 2.5 hours, and imaging acquisition was performed over the last 30 minutes.

- The primary endpoint (percentage of central 5-HT$_{2A}$ receptor occupancy) was calculated regionally using the percentage reduction in binding potential (BP_F, BP_{ND}) at each postdose PET scan from baseline
  - Global receptor occupancy was calculated from a Lassen plot
- [^{18}F]altanserin PET scans and blood sample data were quantitatively analyzed to assess the receptor occupancy as a function of ACP-204 or pimavanserin plasma concentrations for each postdose PET scan
- Additionally, the relationship between ACP-204 and pimavanserin plasma concentrations and the 5-HT$_{2A}$ receptor occupancy was determined by fitting the global receptor occupancy data to a single specific binding site model with a Hill slope fixed at 1 and a fixed maximum at 100% according to the following equation, where *h* is the Hill slope (=1), *X* is the average plasma concentration, and *K* is the EC_{50}

$$Occupancy = (100\% \times X^h) / (K^h + X^h)$$

- Safety was assessed via the collection and review of treatment-emergent adverse events (TEAEs), physical examination, vital signs, electrocardiograms, and laboratory test parameters
- Formal statistical calculations of sample size were not performed

RESULTS

- Of the 16 patients evaluated, the mean age was 44.0 years in the ACP-204 cohorts and 37.7 years in the pimavanserin cohorts; most patients were Black/African American (56%) or White (31%)
- The mean (±SD) global 5-HT$_{2A}$ occupancies following 20 mg of ACP-204 were 103% (±15%) and 102% (±13%) at 4 and 26 hours postdose, respectively, and following 10 mg of ACP-204, were 95% (±4%), 86% (±3%), 80% (±2%), and 62% (±8%) at 4, 26, 50, and 74 hours postdose, respectively (**Table 1**)
  - The mean (±SD) global 5-HT$_{2A}$ occupancies for 34 mg of pimavanserin were 91% (±4%), 90% (±1%), 86% (±6%), and 50% (±13%) at 6, 54, 168, and 288 hours postdose, respectively

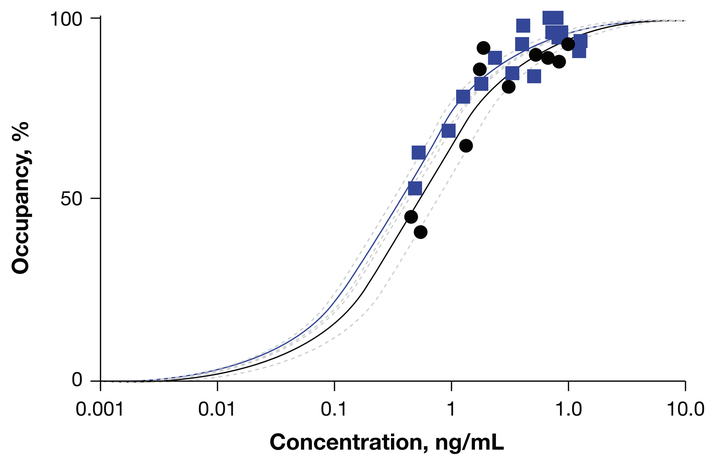
Table 1. Summary of ACP-204 and Pimavanserin 5-HT$_{2A}$ Receptor Occupancy Estimated Using V_T (Global) and BP_P (Regional) Measures Across Cohorts

Cohort	Subject	Global occupancy (V_T), %		Mean occupancy (BP_P), %	
		4 h	**26 h**	**4 h**	**26 h**
ACP-204 20 mg	ACP204_02	120	117	121	119
	ACP204_03	95	93	100	95
	ACP204_04	94	96	96	98
	Mean (±SD)	103 (±15)	102 (±13)	106 (±13)	104 (±13)
		4 h	**26 h**	**4 h**	**26 h**
ACP-204 10 mg	ACP204_07	98	85	100	84
	ACP204_08	96	89	98	91
	ACP204_09	91	84	92	85
	Mean (±SD)	95 (±4)	86 (±3)	97 (±4)	87 (±4)
		50 h	**74 h**	**50 h**	**74 h**
ACP-204 10 mg	ACP204_13	82	69	84	71
	ACP204_18	79	53	73	47
	ACP204_19	78	63	80	64
	Mean (±SD)	80 (±2)	62 (±8)	79 (±6)	61 (±12)
		6 h	**54 h**	**6 h**	**54 h**
Pimavanserin 34 mg	ACP204_21	93	90	94	92
	ACP204_22	88	89	89	88
	Mean (±SD)	91 (±4)	90 (±1)	92 (±4)	91 (±2)
		168 h	**288 h**	**168 h**	**288 h**
Pimavanserin 34 mg	ACP204_23	86	45	87	46
	ACP204_24	92	41	93	41
	ACP204_27	81	65	85	67
	Mean (±SD)	**86 (±6)**	**50 (±13)**	**88 (±4)**	**51 (±14)**

BP_P, binding potential (ratio of specific brain uptake to parent plasma concentration of radiotracer); d, days; h, hours; SD, standard deviation; V_T, total volume of distribution (ratio of total brain uptake to parent plasma concentration of radiotracer).

- Based on the occupancies and plasma concentrations of the drug at each of the scanning time points, the EC_{50} values for ACP-204 and pimavanserin were calculated to be 0.37 ng/mL (95% confidence interval [CI]: 0.31 to 0.44 ng/mL) and 0.55 ng/mL (95% CI: 0.40 to 0.75 ng/mL), respectively (**Figure 2**)

Figure 2. Comparison of Plasma Concentration-Occupancy Relationship Modeled With a Single-Site Specific Binding With a Hill Slope (=1) for ACP-204 and Pimavanserin



CI, confidence interval; EC_{50}, half maximal effective concentration; EC_{90}, 90% maximal effective concentration.

- Only 1 TEAE (pharyngitis) was observed across all cohorts but was determined to be unrelated to treatment
  - No serious TEAEs or clinically meaningful changes in physical examination, vital signs, or electrocardiograms results were reported

CONCLUSIONS

- The administration of ACP-204 resulted in dose- and plasma concentration–dependent occupancy of central 5-HT$_{2A}$ receptors
- ACP-204 demonstrated greater potency than pimavanserin, as reflected in IC_{50} and IC_{90} values, and was well predicted by a single specific binding site model
- Single doses of 10 and 20 mg of ACP-204 were safe and generally well tolerated in healthy adult males

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DISCLOSURES
BR, **EB**, **XF**, **BD**, **SP**, **MD**, and **PZ** are employees of Acadia and may hold stock and/or stock options in Acadia.

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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