Safety, Tolerability, and Pharmacokinetics of APD371, a Highly Selective CB_2 Agonist, in Healthy Adults

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INTRODUCTION

- Chronic pain affects approximately one-third of the US population[1]
- Cannabinoids can be used to effectively manage chronic pain,[2] but their use is limited by unwanted effects on perception, mood, and behavior that result largely from activation of the cannabinoid 1 (CB_1) receptor[3]
  - The CB_1 receptor is found throughout the peripheral and central nervous system (CNS)[4]
  - In contrast, the cannabinoid 2 (CB_2) receptor is expressed mainly in the periphery, including cells of the immune system, microglia, peripheral neurons, and dorsal root ganglion,[4] as well as in gastrointestinal tract immune and epithelial cells[5]
- Some types of chronic pain are inflammatory in nature[6]
  - CB_2 receptor activation has been shown to be anti-inflammatory[6]
- The CB_2 receptor is an ideal potential analgesic target to address inflammatory pain while minimizing the psychotropic effects associated with currently used nonspecific cannabinoids
- Many drugs designed to target the CB_2 receptor have elicited clinical symptoms consistent with CB_1 agonism, have resulted in dose-limiting safety issues, and failed in clinical trials; this is possibly because of drug-specific pharmacodynamic profiles: the drugs were not full agonists nor highly selective for the CB_2 receptor[7,8]
- APD371 is a highly selective, peripherally restricted, full agonist for the CB_2 receptor[6]
  - APD371 was shown to fully bind the human CB_2 receptor at concentrations over 1000-fold less than that required to bind CB_1[6]
  - APD371 was shown to alleviate pain in a monosodium iodoacetate–induced mouse model of osteoarthritic joint pain[6]

OBJECTIVES

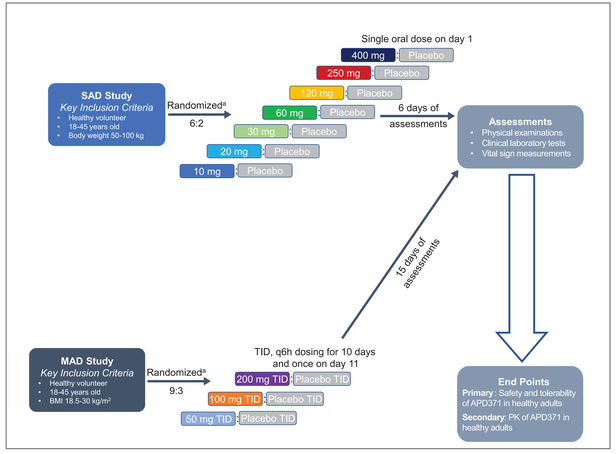
- Assess the safety, tolerability, and pharmacokinetics (PK) of a single ascending dose (SAD) or multiple ascending doses (MAD) of APD371 in healthy volunteers

METHODS

Study Designs

- The SAD and MAD studies were both phase 1, single-site, randomized, double-blind, placebo-controlled, dose-escalation studies of APD371 in healthy adult subjects 18-45 years old (**Figure 1**)

Figure 1. SAD and MAD study designs.



BMI, body mass index; MAD, multiple ascending dose; PK, pharmacokinetics; q6h, every 6 hours; SAD, single ascending dose; TID, 3 times a day.
[a]Subsequent cohorts were dosed upon adequate safety findings in the previous dose cohort.

- Analysis of APD371 and metabolites M1–M5 (SAD) and M1, M2, and M4 (MAD) in plasma and APD371 in urine was performed by Frontage Laboratories, Inc. (Exton, PA), using validated liquid chromatography-tandem mass spectrometry methods. The lower limit of quantification was 0.5 ng/mL in plasma and 2.00 ng/mL in urine

RESULTS

Subjects

- 56 healthy volunteers were enrolled in the SAD study, and 36 healthy volunteers were enrolled in the MAD study
- Demographics and baseline characteristics were similar across treatment groups within each study (**Table 1**)

Table 1. Demographics and Baseline Characteristics in the SAD (top) and MAD (bottom) Studies

		APD371 SAD						
Parameter	Placebo n = 14	10 mg n = 6	20 mg n = 6	30 mg n = 6	60 mg n = 6	120 mg n = 6	250 mg n = 6	400 mg n = 6
Age, mean (SD), years	29.9 (7.4)	25.3 (5.6)	27.8 (8.5)	25.3 (5.6)	25 .5 (3.3)	27.0 (5.5)	22.0 (2.5)	22.7 (3.2)
Race, n (%)								
Asian	0	0	0	0	0	0	0	1 (16.7)
Black or African American	1 (7.1)	0	0	0	0	0	0	0
White	13 (92.9)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	5 (83.3)
Ethnicity, n (%)								
Hispanic or Latino	3 (21.4)	1 (16.7)	1 (16.7)	3 (50.0)	2 (33.3)	3 (50.0)	3 (50.0)	2 (33.3)
Not Hispanic or Latino	11 (78.6)	5 (83.3)	5 (83.3)	3 (50.0)	4 (66.7)	3 (50.0)	3 (50.0)	4 (66.7)
Female, n (%)	7 (50.0)	4 (66.7)	3 (50.0)	3 (50.0)	3 (50.0)	3 (50.0)	2 (33.3)	4 (66.7)
Weight, mean (SD), kg	74.7 (8.0)	69.6 (14.0)	73.7 (9.6)	70.9 (10.7)	74.1 (13.8)	75.4 (13.8)	85.5 (9.8)	76.2 (12.8)
BMI, mean (SD), kg/m²	26.3 (1.9)	24.1 (3.4)	25.0 (3.2)	25.2 (5.3)	24.7 (3.5)	26.5 (3.3)	27.6 (3.7)	27.5 (3.2)

		APD371 MAD			
Parameter	Placebo TID n = 9	50 mg TID n = 9	100 mg TID n = 9	200 mg TID n = 9	All MAD Subjects n = 36
Age, mean (SD), years	33.6 (9.2)	34.6 (8.2)	33.0 (7.4)	31.9 (9.8)	33.3 (8.4)
Race, n (%)					
Asian	0	0	1 (11.1)	0	1 (2.8)
Black or African American	2 (22.2)	5 (55.6)	6 (66.7)	5 (55.6)	18 (50.0)
Multiple	0	1 (11.1)	0	1 (11.1)	2 (5.6)
White	7 (77.8)	3 (33.3)	2 (22.2)	3 (33.3)	15 (41.7)
Ethnicity, n (%)	0	0	1 (11.1)	0	1 (2.8)
Hispanic or Latino	5 (55.6)	3 (33.3)	3 (33.3)	1 (11.1)	12 (33.3)
Not Hispanic or Latino	4 (44.4)	6 (66.7)	6 (66.7)	8 (88.9)	24 (66.7)
Female, n (%)	6 (66.7)	6 (66.7)	5 (55.6)	4 (44.4)	21 (58.3)
Weight, mean (SD), kg	71.4 (9.5)	79.4 (16.3)	75.9 (11.7)	76.1 (18.1)	75.7 (14.0)
BMI, mean (SD), kg/m²	25.9 (2.3)	26.8 (3.0)	26.7 (2.3)	25.4 (3.7)	26.2 (2.8)

BMI, body mass index; MAD, multiple ascending dose; SAD, single ascending dose; SD, standard deviation; TID, 3 times a day.

Safety and Tolerability

- 45 treatment-emergent adverse events (TEAEs) were reported by 22 subjects (39.3%) in the SAD study (**Table 2**)
  - 91.1% were mild in severity, and 53% were deemed unrelated to the study drug
  - Of the most common TEAEs (**Table 2**), dry mouth and somnolence were only reported in the higher dose groups (250 mg and 400 mg)

Table 2. Adverse Events That Were Reported in ≥5% of Subjects Who Received APD371 in the SAD Study

		APD371						
Preferred Term	Placebo n = 14	10 mg n = 6	20 mg n = 6	30 mg n = 6	60 mg n = 6	120 mg n = 6	250 mg n = 6	400 mg n = 6
TEAEs reported, n	4	6	1	2	2	9	5	16
Subjects reporting any TEAE, n (%)	3 (21.4)	3 (50.0)	1 (16.7)	1 (16.7)	2 (33.3)	5 (83.3)	2 (33.3)	5 (83.3)
Somnolence	0	0	0	0	0	0	0	4 (66.7)
Dry mouth	0	0	0	0	0	0	2 (33.3)	2 (33.3)
Dizziness	1 (7.1)	0	0	1 (16.7)	0	0	0	2 (33.3)
Diarrhea	0	1 (16.7)	0	0	0	2 (33.3)	0	0
Headache/sinus headache	0	3 (50.0)	0	0	0	0	0	0

TEAE, treatment-emergent adverse event.
Note: For each adverse event category, subjects reporting more than 1 occurrence were only counted once. Sinus headache was determined by the opinion of a study investigator, considering the details of the history and physical examination.
MedDRA v 16.1 was used as the adverse event coding dictionary.

- 17 TEAEs were reported by 10 subjects (27.8%) in the MAD study; all were mild (**Table 3**).

Table 3. Adverse Events Reported in Any Subject in the MAD Study

Preferred Term	Placebo, TID n = 9	Total APD371, TID n = 27
Subjects reporting any TEAE	3 (33.3)	7 (25.9)
Headache	0	2 (7.4)
Nausea	0	2 (7.4)
Constipation	0	1 (3.7)
Deafness bilateral	0	1 (3.7)
Dysmenorrhea	0	1 (3.7)
Dyspepsia	0	1 (3.7)
Eructation	0	1 (3.7)
Musculoskeletal stiffness	0	1 (3.7)
Somnolence	0	1 (3.7)
Thirst	0	1 (3.7)
Back pain	1 (11.1)	1 (3.7)
Neck pain	1 (11.1)	1 (3.7)
Eyelid edema	1 (11.1)	0

MAD, multiple ascending dose; TEAE, treatment-emergent adverse event ; TID, 3 times a day.
Note: For each adverse event category, subjects reporting more than 1 occurrence were only counted once.

- 1 subject in the MAD study discontinued because of TEAEs (mild thirst and mild somnolence; 200-mg TID group); none in the SAD study withdrew because of TEAEs
- No deaths or serious TEAEs were reported in either study
- No disturbances in vital signs were clinically significant or resulted in any TEAEs, although some variable changes were recorded for heart rate, blood pressure, and PR interval duration

PHARMACOKINETICS

- Systemic exposures of APD371 as measured by maximum plasma concentration (C_{max}) (both studies), area under the concentration-time curve from time 0 to infinity (AUC_{inf}) (both studies), and AUC from time 0 to 24 hours ($AUC_{0\text{-}24}$; SAD study only) increased with dose in a manner that was less than dose proportional (**Figure 2** and **Table 4**, SAD; **Figure 3** and **Table 5**, MAD)

Figure 2. Pharmacokinetics of APD371 after a single dose.

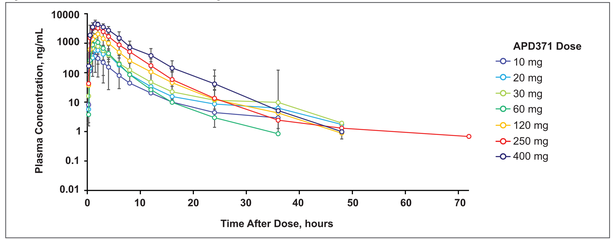
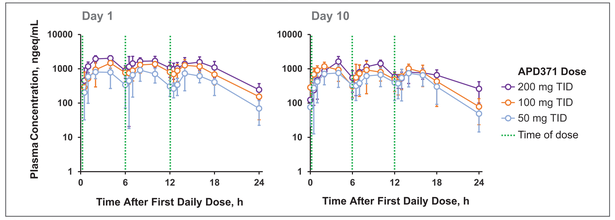


Figure 3. Pharmacokinetics of APD371 on day 1 and day 10 (steady state) of TID dosing.



TID, 3 times a day.

- The median time to reach C_{max} was approximately 1.5 hours in the SAD study (**Table 4**) and 2 to 4 hours across all dose groups and days dosed in the MAD study (**Table 5**)
- The terminal half-life ($t_{1/2}$) for plasma APD371 ranged from 3.11 to 4.23 hours across dose groups in the SAD study (**Table 4**) and 3.79 to 5.06 hours across dose groups in the MAD study (**Table 5**)

Table 4. Summary of APD371 Plasma and Urine PK Parameters After a Single Dose

Dose	10 mg	20 mg	30 mg	60 mg	120 mg	250 mg	400 mg
t_{max}[a] mean (CV%), h	1.02 (0.52-1.53)	1.52 (1.02-2.10)	1.52 (1.02-2.02)	1.53 (1.00-2.02)	1.53 (1.02-2.02)	1.52 (1.52-2.02)	1.51 (0.52-2.02)
C_{max}, ng/mL	351 (69.8)	583 (52.6)	874 (39.0)	1,150 (30.2)	2,000 (51.9)	3,730 (15.5)	4,590 (28.5)
AUC_{inf}, ng·h/mL	1,190 (89.6)	2,100 (98.7)	3,280 (62.4)	3,760 (32.4)	7,530 (67.7)	16,500 (14.1)	21,800 (35.8)
V_z/F, liters	44.8 (54.4)	64.3 (44.7)	44.4 (19.3)	78.0 (21.5)	73.2 (28.4)	75.2 (21.5)	92.1 (26.5)
CL/F, L/h	9.90 (52.5)	11.4 (52.4)	10.0 (39.2)	17.1 (46.1)	17.3 (34.9)	15.3 (16.1)	19.3 (33.8)
$t_{1/2}$, h	3.56 (38.9)	4.23 (20.5)	3.52 (39.7)	3.42 (24.5)	3.11 (23.3)	3.53 (32.9)	3.43 (18.5)
CL_R,[b] L/h	0.0859 (40.7)	0.0834 (58.6)	0.0980 (37.4)	0.140 (29.7)	0.126 (24.9)	0.122 (17.2)	0.150 (43.9)

AUC_{inf}, area under the plasma concentration-time curve from time 0 to infinity; C_{max}, maximum plasma concentration; CL/F, apparent total body clearance; CL_R, apparent renal clearance; CV(%), coefficient of variation; $t_{1/2}$, time to half maximal plasma concentration; t_{max}, time to maximum plasma concentration; V_z/F, apparent volume of distribution.
[a]Geometric mean (CV%) for C_{max} and AUC, median (min-max) for t_{max}, arithmetic mean and CV% for all other parameters.
[b]All parameters calculated from plasma except CL_R, which was calculated from plasma and urine.

- After 10 days of TID dosing, there was no accumulation of APD371 in plasma, as measured by $AUC_{0\text{-}24}$ day 10/day 1 accumulation indices (**Table 5**)

Table 5. Summary of APD371 Plasma and Urine PK Parameters on Day 1 of TID Dosing and at Steady State[a,b]

Dose	t_{max},[c] h	C_{max},[c] ng/mL	C_{max} Accumulation Index[d]	$AUC_{0\text{-}24}$ ng·h/mL	$AUC_{0\text{-}24}$ Accumulation Index[d]	CL_R L/h	CL/F L/h
Day 1							**Day 11**
50 mg TID	2.00 (1.00-4.00)	1,060 (34.8)		11,300 (39.4)		0.0529 (24.4)	14.3 (45.1)
100 mg TID	4.00 (2.00-4.00)	1,500 (29.5)		19,500 (36.3)		0.0603 (48.0)	24.8 (48.0)
200 mg TID	4.00 (2.00-4.03)	2,150 (19.2)		28,800 (23.9)		0.0851 (30.9)	32.6 (32.2)
Day 10 (steady state)							
50 mg TID	3.00 (1.00-4.00)	922 (46.0)	0.938 (47.7)	11,300 (38.1)	0.992 (20.0)	0.0576 (34.7)	
100 mg TID	2.00 (1.00-4.00)	1,210 (27.7)	0.859 (29.7)	14,000 (43.5)	0.748 (11.9)	0.0775 (49.0)	
200 mg TID	4.00 (2.00-4.00)	1,650 (29.6)	0.793 (22.5)	17,900 (27.7)	0.604 (8.81)	0.0938 (25.9)	

$AUC_{0\text{-}24}$, area under the plasma concentration-time curve from time 0 to 24 hours; C_{max}, maximum plasma concentration; CL/F, apparent total body clearance; CL_R, apparent renal clearance; CV%, coefficient of variation; t_{max}, time to maximum plasma concentration.
[a]Geometric mean and CV% for C_{max} and AUC, median (min-max) for t_{max}, arithmetic mean and CV% for all other parameters; n = 8-9.
[b]All parameters calculated from plasma except CL_R, which was calculated from plasma and urine.
[c]T_{max} and C_{max} parameters apply only to the first dose of the day.
[d]Accumulation index was calculated as day 10/day 1.

- APD371 plasma concentration reached steady state within 4 days across all dose groups, as measured by the log-transformed slopes of predose C_{trough} values on days 4, 6, 8, and 10
- Systemic exposures of all tested metabolites increased in a less than dose proportional manner; the combined half-life of active metabolites and APD371 (M1 + M4 + APD371) ranged from 7.67 to 9.01 hours in the MAD study

SUMMARY AND CONCLUSIONS

- APD371 is a highly selective, full agonist at the CB_2 receptor
- APD371 was safe and well tolerated in the SAD and MAD studies and did not exhibit the psychotropic effects commonly seen with cannabinoids
- Adverse events were mostly mild, and no serious adverse events occurred in either study
- APD371 plasma concentrations were less than dose proportional in both studies, and no accumulation was measured after 10 days of TID dosing in the MAD study
- The half-life of APD371 was consistent across studies at approximately 4 hours and supports the TID dosing regimen used in the MAD study, although twice daily dosing may be explored in future studies
- APD371 may provide a preferred therapeutic approach for chronic pain
- APD371 is currently being evaluated in a phase 2 clinical trial for visceral pain associated with Crohn's disease

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