Poster #1860
Abstract #64127

Phase 1 Study to Assess Safety, Tolerability and Pharmacokinetics of Single and Multiple Oral Doses of APX001 and to Investigate the Effect of Food on APX001A Bioavailability

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ABSTRACT

Background: APX001 is a first-in-class, intravenous (IV) and oral (PO) broad-spectrum antifungal agent in clinical development for the treatment of invasive fungal infections (IFIs) due to *Candida, Aspergillus* and rare molds. The active moiety APX001A inhibits Gwt1, an early step in glycosylphosphatidylinositol (GPI) anchor biosynthesis. Excellent *in vivo* efficacy has been demonstrated in murine models of IFIs with APX001A AUC_{0-24} target exposures ~80 µg.hr/mL.

Methods: Eight subjects in Cohort 1a were randomized in a 6:2 ratio to receive APX001 or placebo. Single doses of IV 200 mg were infused over 3 hours followed by single (tablet) doses of 100, 300, and 500 mg, each separated by a 14-day washout period. Ten subjects in Cohort 1b were randomized in a 8:2 ratio to receive either APX001 or placebo. A single PO (tablet) dose of 400 mg was administered under fed and fasted conditions, each separated by a 14-day washout period. MAD Cohorts 2 and 3 were comprised of eight subjects randomized in a 6:2 ratio to receive APX001 or placebo. Subjects received PO (tablet) doses of 500 and 1000 mg daily for 14 days. Pharmacokinetic (PK) parameters for APX001A in plasma were calculated using non-compartmental analysis. Safety monitoring and intense PK sampling occurred throughout the trial. A safety committee reviewed the PK and safety data to determine dose escalation steps.

Results: Plasma exposure to APX001A was linear, dose proportional with low intersubject variability and a half-life of ~2.5 days. Accumulation of APX001A was observed in the MAD cohorts. After 14 days of dosing at 500 and 1000 mg AUC_{0-24} were 192 and 325 µg.hr/mL, respectively. The oral bioavailability was >90%. Administration of APX001 with a high fat, high calorie meal had no effect on the rate or extent of absorption. APX001 was well tolerated across all doses with no clinically significant adverse events observed and no dose limiting toxicities. Most of the AEs were mild, transient and required no treatment.

Conclusion: APX001 given orally is highly bioavailable, has no food effect and can exceed target exposures of APX001A for efficacy against *Candida* and *Aspergillus* at doses that are safe and well tolerated.

METHODS

Study Design:

- Phase 1 double-blind, placebo-controlled, randomized study to investigate the safety, tolerability, pharmacokinetics, bioavailability and food effect of single doses of APX001 administered intravenously and orally.
- Healthy male and female subjects aged 18 to 55 years were enrolled.
- A Safety Review Committee reviewed safety and PK data to determine the appropriateness of dose escalation (rules defined *a priori* in the protocol).

Refer to **Methods** under Abstract section for details on cohort design and dose levels.

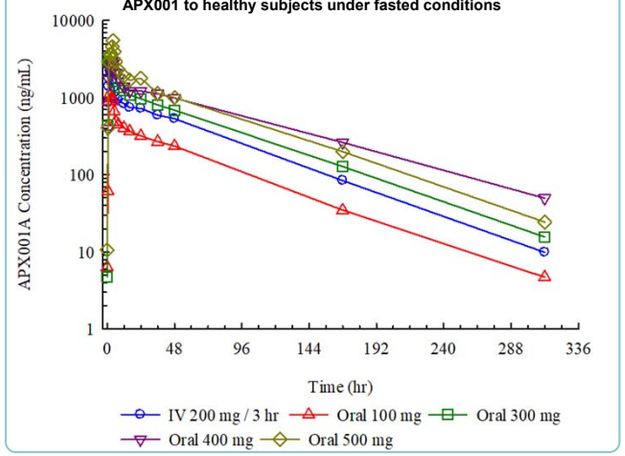
Study Objectives:

- Evaluate the safety, tolerability, and pharmacokinetic parameters of single and multiple doses of APX001 administered orally in healthy volunteers
- Determine the relative bioavailability of active moiety APX001A after a single IV dose of prodrug APX001, compared to the bioavailability of APX001A after a single oral dose of APX001
- Determine the effect of food on the pharmacokinetics of APX001 and APX001A following a single oral administration of APX001
- Evaluate the time-dependency, if any, of the pharmacokinetics of APX001A following repeated oral administration of APX001
- Explore the APX001 oral dose required to attain APX001A target plasma exposures (AUC_{0-24}) required for clinical efficacy against *Candida*, *Aspergillus* and the hard-to-treat rare molds (*Scedosporium*, *Fusarium* and Mucorales) invasive fungal infections

RESULTS

- SAD Cohorts 1a and 1b: After IV and oral administration of APX001 at single doses from 100 mg to 500 mg, there were dose-proportional increases in the geometric mean APX001A plasma concentrations and values for Cmax, AUC(0-t), and AUC(inf).

Figure 1: Geometric mean plasma concentrations of APX001A after intravenous infusion of 200 mg APX001 over 3 hours and oral doses of 100 mg to 500 mg APX001 to healthy subjects under fasted conditions



- Median values for Tmax ranged from 2.00 hr to 3.00 hr with consistent ranges for the 4 oral doses.
- Geometric mean values for t1/2 ranged from 44.9 hr to 64.7 hr for the four oral treatments.
- Absolute bioavailability of APX001A ranged from 90.6% to 101.2%, indicating essentially complete absorption of APX001 and conversion to APX001A.

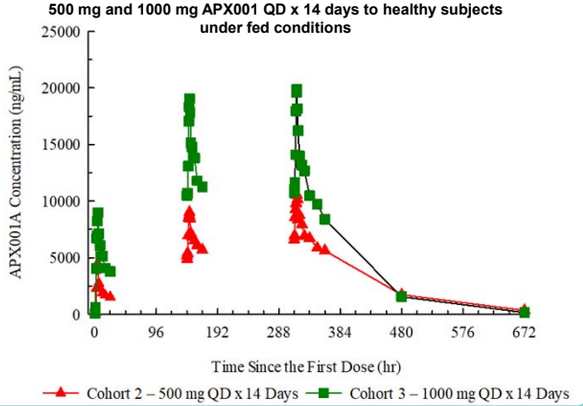
Table 1: Summary of PK parameters for APX001A (Cohorts 1a & 1b – single ascending dose)

Parameter	Cohort 1a, 1b (Fasted)				
	200 mg 3 hr IV	100 mg Oral	300 mg Oral	400 mg Oral	500 mg Oral
Cmax (ng/mL)	2,635	1,302	3,754	4,252	6,407
Tmax (hr)	3.00	2.00	2.50	2.50	3.00
AUC(0-24) (hr x ng/mL)	24,387	11,757	35,613	39,979	59,001
AUC(0-t) (hr x ng/mL)	86,300	39,049	118,208	170,191	196,804
AUC(inf) (hr x ng/mL)	87,530	39,644	122,230	177,134	204,624
CL or CL/F: (mL/hr)	1,748	1,930	1,878	1,728	1,870
CL or CL/F: (mL/hr/kg)	22.6	25.0	24.3	25.1	25.1
t1/2 (hr)	49.1	49.5	52.5	64.7	44.9
F (%)	-	90.6	93.1	101.2	93.5

RESULTS (cont'd)

- MAD Cohorts 2 and 3: There was an approximate 2-fold increase in the geometric mean APX001A values for Cmax and AUC_{0-24} on Days 1, 7, and 14, suggesting dose-proportional pharmacokinetics after multiple doses.
- There was good agreement with respect to the geometric mean APX001A values for Cmax and AUC_{0-24} on Day 1 for the two cohorts administered 500 mg – Cohort 2 and Cohort 1a / Period D in the SAD part of the study.

Figure 2: Geometric mean plasma concentrations of APX001A after oral doses of 500 mg and 1000 mg APX001 QD x 14 days to healthy subjects under fed conditions



- Median Tmax ranged from 1.00 hr to 4.50 hr across doses and study days but with overlapping ranges, suggesting no apparent change with continued dosing.
- Median accumulation ratios based on Cmax and AUC_{0-24} were 1.99 and 2.95, respectively.
- Geometric mean values for t1/2 ranged from 52.6 hr to 73.4 hr for the two cohorts.

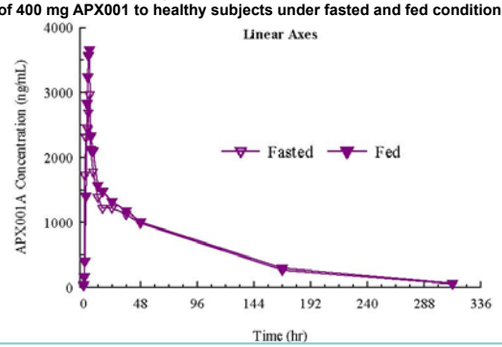
Table 2: Summary of PK parameters for APX001A (Cohorts 2 & 3 - multiple ascending dose)

Parameter		Cohort 2 / 500 mg QD	Cohort 3 / 1000 mg QD
Day 1	Cmax (ng/mL)	6,176	10,589
	Tmax (hr)	4.00	4.50
	AUC(0-24) (hr x ng/mL)	50,735	118,823
Day 7	Cmax (ng/mL)	10,876	21,332
	Tmax (hr)	3.76	4.00
	AUC(0-24) (hr x ng/mL)	154,461	315,557
Day 14	Cmax (ng/mL)	11,959	21,275
	Tmax (hr)	3.75	3.77
	AUC(0-24) (hr x ng/mL)	191,382	325,842
	CL: (mL/hr)	1,999	2,348
	CL: (mL/hr/kg)	27.7	34.9
	t1/2 (hr)	73.4	52.6

RESULTS (cont'd)

- Cohort 1b (Food Effect): The geometric mean APX001A values for Cmax, AUC(0-t), and AUC(inf) were slightly higher after administration with food.

Figure 3: Geometric mean plasma concentrations of APX001A after oral doses of 400 mg APX001 to healthy subjects under fasted and fed conditions



- Least squares geometric mean ratios were ~106% for Cmax, AUC(0-t), & AUC(inf).
- Although the median Tmax under fed conditions, 3.75 hr, was longer than under fasted conditions, 2.50 hr, the ranges were comparable.
- Geometric mean values for t1/2 were also comparable.
- Taken as a whole, administration of APX001 with a high fat/high calorie meal had no significant effect on the bioavailability of APX001A.

Table 3: Summary of PK parameters for APX001A after oral doses of 400 mg APX001 to healthy subjects under fasted and fed conditions

Parameter	Cohort 1b – 400 mg		Geometric Mean Ratio
	Fasted	Fed	
Cmax (ng/mL)	4,252	4,520	106.29
Tmax (hr)	2.50	3.75	
AUC(0-24) (hr x ng/mL)	39,979	43,597	
AUC(0-t) (hr x ng/mL)	170,191	180,401	106.00
AUC(inf) (hr x ng/mL)	177,134	188,027	106.15
CL/F: (mL/hr)	1,728	1,628	
CL/F: (mL/hr/kg)	25.1	23.7	
t1/2 (hr)	64.7	67.5	
F (%)	101.2	107.4	

CONCLUSIONS

All doses of APX001 were safe and well tolerated. The majority of the adverse events were mild, transitory and resolved without intervention. No dose-limiting toxicities were observed and no AEs or laboratory safety test results met any of the *a priori* rules that prevented dose escalation. The maximum tolerated dose was not determined/reached in this study. Target APX001A plasma concentrations required for clinical efficacy in invasive fungal infections were exceeded. These drug characteristics suggest that APX001 has potential as a treatment option for patients with life-threatening fungal infections.