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First-in-Human Study to Assess Safety, Tolerability and Pharmacokinetics of APX001 Administered by Intravenous Infusion to Healthy Subjects

M. R. Hodges [1]*, E. Ople [1], K. J. Shaw [1], R. Mansbach [1], S. van Marle [2], E. van Hoogdalem [2], P. Wedel [1], and W. Kramer [1]
[1] Amplyx Pharmaceuticals Inc., San Diego, CA, USA; [2] PRA Health Sciences, Groningen, Netherlands

*Michael R. Hodges MBBS, BSc
Amplyx Pharmaceuticals Inc.
mhodges@amplyx.com

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 $AUC_{0\text{-}24}$ target exposures ~80 µg.hr/mL.

Methods: There were six single ascending dose (SAD) and four multiple ascending dose (MAD) cohorts, eight subjects/cohort. Subjects were randomized in a 6:2 ratio to receive 3-hour IV infusions of APX001 or placebo. SAD Cohorts 1-6 received single doses of 10, 30, 100, 200, 275, and 350 mg, respectively. MAD Cohorts 7-10 received doses of 50, 150, 300, and 600 mg, respectively, once 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. As expected from the half-life and dosing frequency, accumulation of APX001A was observed in the MAD cohorts. A single APX001 dose of 350 mg maintained drug levels above the minimum inhibitory concentration (MIC) of *Candida* and *Aspergillus* for one week. The 600 mg/day $AUC_{0\text{-}24}$ on Day 14 was 245 µg.hr/mL.
APX001 was well tolerated across all doses with no clinically significant adverse events observed. One subject discontinued due to the adverse event (AE) of flu. There were no dose limiting toxicities. Most of the AEs were mild, transient and required no treatment. The most common AE was headache.

Conclusion: Target exposures of APX001A for efficacy against *Candida* and *Aspergillus* were exceeded at doses that are safe and well tolerated.

METHODS

Study Design:
- First in human, randomized, double-blind, placebo-controlled single ascending dose (SAD) and multiple ascending dose (MAD) escalation study enrolling healthy male and female subjects, aged 18 to 55 years.
- Eight subjects in each cohort were randomized to receive either APX001 or placebo in a 6:2 ratio, with doses infused over 3 hours (see Methods section above for specific dose levels).
- Two sentinel subjects in each cohort received their dose(s) prior to the remaining subjects in the cohort.
- A Safety Review Committee reviewed sentinel safety and PK data from the sentinel and remaining subjects to determine the appropriateness of continued dosing and dose escalation, respectively (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 by intravenous (IV) infusion in healthy volunteers
- Determine the maximum tolerated dose
- Explore the safety profile of APX001 in relation to the duration of infusion observed at APX001A target plasma exposures ($AUC_{0\text{-}24}$) required for clinical efficacy
- Explore the APX001 dose and dose regimen required to attain APX001A target plasma exposures ($AUC_{0\text{-}24}$) required for clinical efficacy against *Candida*, *Aspergillus* and the hard-to-treat rare molds (*Scedosporium*, *Fusarium*, and Mucorales) invasive fungal infections

Study Endpoints and Assessments:
- Safety and tolerability: Evaluation of adverse events, physical examinations, vital signs, laboratory safety tests, urinalysis and 12-lead electrocardiograms
- Pharmacokinetics: as appropriate – non-compartmental analysis (including $AUC_{0\text{-}24}$, $AUC_{0\text{-}t}$, AUC_{inf}, Cmax, Tmax, CL, $t_{1/2}$), and compartmental modeling

Stopping Rules:

Dose Escalation Stopping Rule:
SRC may recommend to Sponsor that dosing to the next higher dose level in either the SAD or MAD part of the study be suspended if any of the following occur:
- Two subjects experience Grade 3 or 4 AE, including laboratory abnormality per CTCAE Version 4.0 that is considered related to study drug.

METHODS (cont'd)

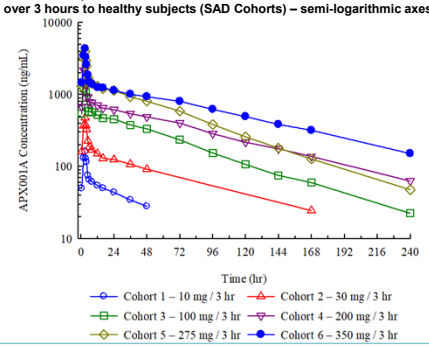
Dose Escalation Stopping Rule (continued):
- One subject experiences a Serious Adverse Event (SAE) that is considered related to study drug.
- The opinion of the SRC is that further dose escalation would pose an inappropriate safety risk.
- Should two subjects experience a Grade 2 AE that is classified by the investigator or SRC as nervous system disorder per CTCAE Version 4.0 and considered related to study drug, then dose escalation cannot occur until the AE in question has resolved.

Subject Stopping Rule:
- SAD: Not applicable for the SAD cohorts since subjects receive a single dose.
- MAD: Subjects may be discontinued from the study drug treatment for any AE, SAE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject.

RESULTS

- SAD Cohorts 1-6: After IV infusion of APX001 at single doses from 10 mg to 350 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 APX001 over 3 hours to healthy subjects (SAD Cohorts) – semi-logarithmic axes



- Geometric mean values for t1/2 ranged from 39.2 hr to 74.9 hr for SAD Cohorts 1-6.
- A single APX001 dose of 350 mg maintained drug levels above the MIC of *Candida* and *Aspergillus* for one week.

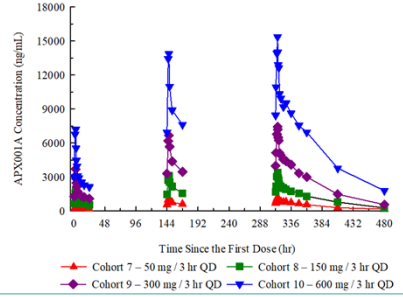
Table 1: Summary of PK parameters for APX001A (SAD Cohorts) – *non-compartmental analysis*

Parameter	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6
Cmax (ng/mL)	161	477	1,444	2,412	3,964	4,326
Tmax (hr)	3.00	3.00	3.00	3.00	3.00	3.00
AUC(0-24) (hr x ng/mL)	1,536	4,325	14,359	20,748	37,066	36,168
AUC(0-t) (hr x ng/mL)	2,379	14,079	47,400	76,000	114,256	153,440
AUC(inf) (hr x ng/mL)	4,048	16,645	50,370	83,169	119,740	173,418
CL: (mL/hr)	1,890	1,379	1,519	1,840	1,757	1,544
CL: (mL/hr/kg)	27.0	19.6	24.8	25.5	25.0	20.9
t1/2 (hr)	39.2	61.0	52.5	67.0	48.6	74.9

RESULTS (cont'd)

- MAD Cohorts 7-10: There was a dose-proportional increase in the geometric mean APX001A plasma concentrations and geometric mean values for Cmax and $AUC_{0\text{-}24}$ on Days 1, 7, and 14 after IV infusion of APX001 at doses of 50 mg to 600 mg QD x 14 days.

Figure 2: Geometric mean plasma concentrations of APX001A after intravenous infusion of APX001 over 3 hours QD x 14 days to healthy subjects (MAD Cohorts)



- Accumulation ratios based on Cmax and $AUC_{0\text{-}24}$ were 1.96 and 5.90, respectively.
- The APX001A geometric mean t1/2 was consistent across the SAD and MAD cohorts, with values for MAD Cohorts 7-10 ranging from 52.6 hr to 69.0 hr.

Table 2: Summary of PK parameters for APX001A (MAD Cohorts) – *non-compartmental analysis*

	Parameter	Cohort 7	Cohort 8	Cohort 9	Cohort 10
Day 1	Cmax (ng/mL)	669	1,865	3,687	7,572
	Tmax (hr)	3.00	3.00	3.00	3.00
	AUC(0-24) (hr x ng/mL)	6,388	19,382	37,059	72,679
Day 7	Cmax (ng/mL)	1,091	3,090	6,654	14,491
	Tmax (hr)	3.00	3.00	3.00	3.03
	AUC(0-24) (hr x ng/mL)	17,566	48,682	104,080	217,089
Day 14	Cmax (ng/mL)	1,182	3,424	7,523	15,364
	Tmax (hr)	3.00	3.02	3.02	3.00
	AUC(0-24) (hr x ng/mL)	20,266	51,907	118,362	245,049
	CL: (mL/hr)	1,888	2,211	1,939	1,873
	CL: (mL/hr/kg)	24.5	27.7	29.0	29.4
	t1/2 (hr)	69.0	52.6	53.1	64.8

CONCLUSIONS

This First-In-Human study demonstrated that all doses of APX001 tested 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 tests met any of the *a priori* rules that prevented dose escalation. The maximum tolerated dose was not determined/reached in this study. Target APX001A exposures for clinical efficacy against *Candida, Aspergillus*, and rare molds were exceeded. These drug characteristics suggest that APX001 has potential as a treatment option for patients with life-threatening fungal infections.