APX001
A novel broad spectrum antifungal agent in development for the treatment of invasive fungal infections

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New antifungal drugs in the pipeline S15

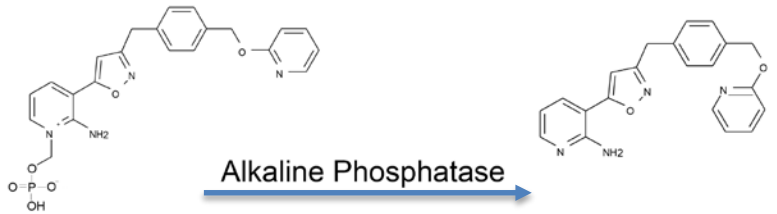
Dr. Michael Hodges on behalf of the Amplyx Pharmaceuticals, Inc. Development Team

Disclosures

- Current position
  - Chief Medical Officer for Amplyx Pharmaceuticals FTE
  - Scientific Advisory Boards Exicure Inc. and Arcturus Therapeutics Inc.

APX001 Key Characteristics

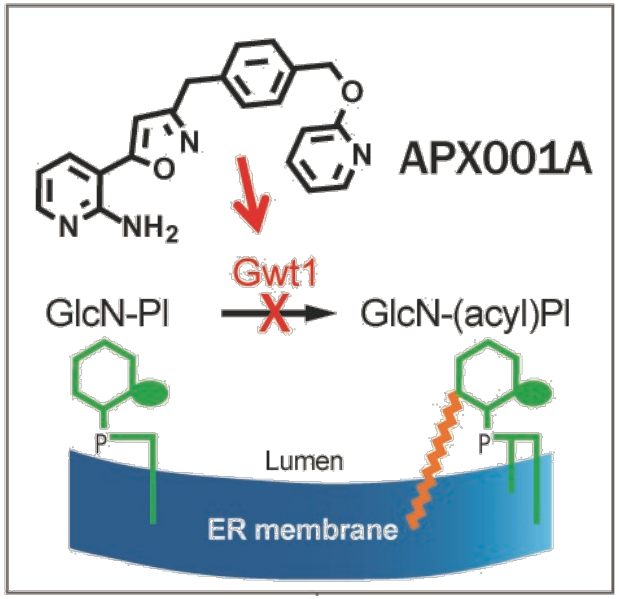
- First in class novel mechanism of action – inhibition of Gwt1[1]
- Broad spectrum yeasts and molds – including *hard-to-treat* resistant isolates
- Oral & IV formulations – 1 hr infusions
- Low DDI liability
- Excellent PK profile – once day dosing with low variability
- Safe and well tolerated over 14-days in healthy volunteers

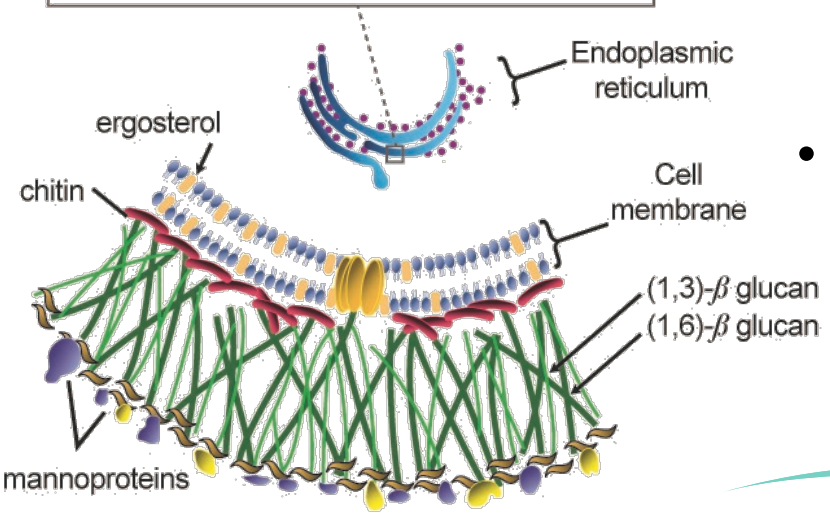


APX001 APX001A

[1] Gwt1 GPI-anchored wall transfer protein 1

APX001A Mechanism of Action





- GPI-anchored proteins (e.g. mannoproteins) provide cell wall integrity, are involved in membrane homeostasis, promote adhesion, pathogenicity and immune evasion
- Gwt1 is essential for the conversion of glucosaminyl phosphatidylinositol glucosaminyl(acyl)phosphatidylinositol, an essential/early step in GPI synthesis
- APX001A is a potent inhibitor of fungal Gwt1 and has no activity vs. related mammalian PIG-W protein

In vitro Activity

- APX001A has low MICs against most strains tested, including strains resistant to existing treatments
- APX001A is broadly active against *Candida* spp. (MIC_{90} ≤0.06 µg/mL)
  - Significant activity vs *C. auris* (MIC_{90} 0.03 µg/mL) - APX001A is the most microbiologically active drug tested
  - Higher MICs against *C. krusei*
- APX001A is broadly active against *Aspergillus* spp. (MEC_{90} ≤0.06 µg/mL)
- APX001A is broadly active against the rare *hard-to-treat* molds
  - Good activity against *Scedosporium* spp. and *Fusarium* spp.
- Activity against resistant organisms (no cross-resistance)
- Synergy *in vitro* and *in vivo*, long PAFE, biofilm prevention
- Low frequency of resistance similar to echinocandins

In vivo Activity

- APX001 has demonstrated activity, both survival and/or decreased fungal burden (kidney, lung, spleen and brain) in a number of immunocompromised (5-FU and CPA) and immunocompetent murine animal models of invasive infection[1] including both pulmonary and disseminated models
  - *Candida albicans, C. tropicalis, C. glabrata, C. auris* [5FU & CPA]
  - *Aspergillus fumigatus, A. flavus* [5FU]
  - Rare molds including *Fusarium solani, Scedosporium prolificans, Rhizopus oryzae* [5FU & CPA]
  - *Cryptococcus neoformans* [CPA]
  - *Coccidioides immitis* [immunocompetent]
- Efficacy driven by AUC/MIC

5-FU 5-Fluorouracil; CPA cyclophosphamide

[1] In addition non invasive VVC and OPC animal models

APX001 Early Clinical Development Plan

Phase 1 program

APX001	Phase	Population & Outcomes	n	Route	Comparator	Objective
101	1	Healthy Volunteers • SAD and MAD • Decreased infusion times • Loading dose	120	IV	Placebo	Safety and PK
102	1	Healthy Volunteers • SAD and MAD • Food effect • DDI “Cocktail” cohort	46	oral	Placebo	Safety and PK
103	1b	AML patients • Multiple doses in target patient population • APX001 in combo with SOC chemo & azole prophylaxis • Supports APX001 low DDI liability attribute	20	IV & oral	none	Safety and PK

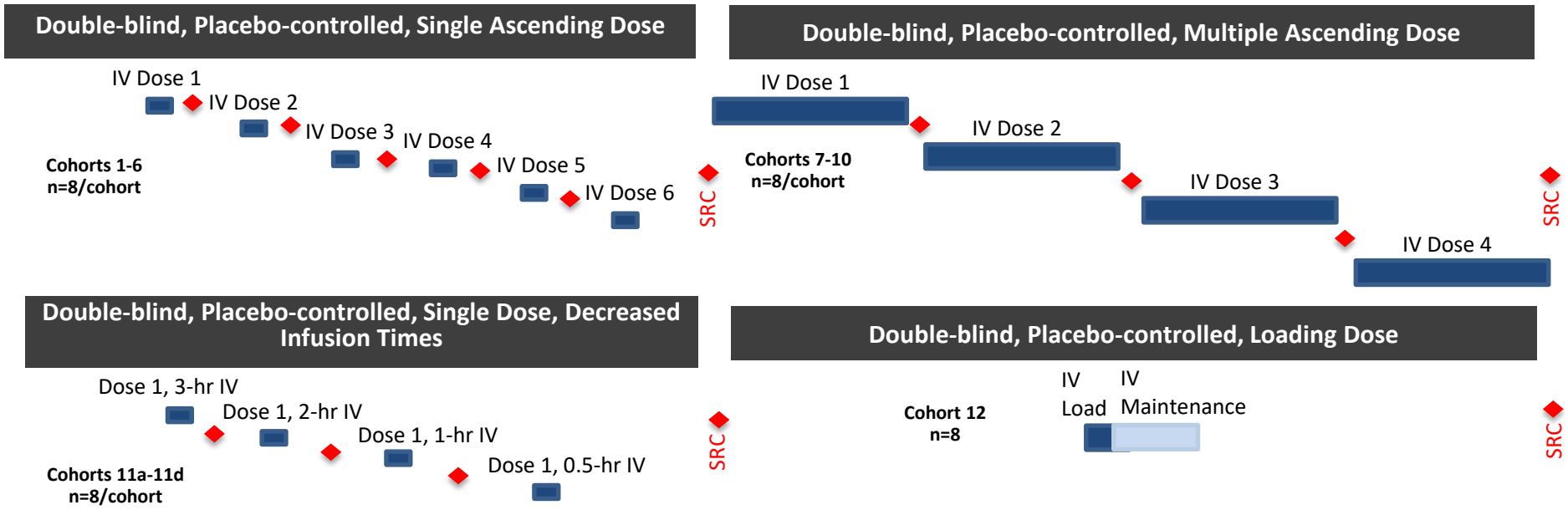
APX001-101 IV Phase 1

Objectives

- First-In-Human, randomized, double-blind, placebo-controlled single ascending dose (SAD) and multiple ascending dose (MAD) escalation study in healthy volunteers
- Different dosing regimens were also evaluated
  - Decreased infusion times
  - Loading dose
- Objectives included
  - evaluation of safety, tolerability, and PK of single and multiple doses of APX001 administered by intravenous (IV) infusion in healthy volunteers
  - exploration of APX001 dose and dose regimen required to attain APX001A target plasma exposures (AUC_{24}) required for clinical efficacy against *Candida*, *Aspergillus* and the hard-to-treat rare molds (*Scedosporium*, *Fusarium* and Mucorales) IFIs

APX001-101 IV Phase 1

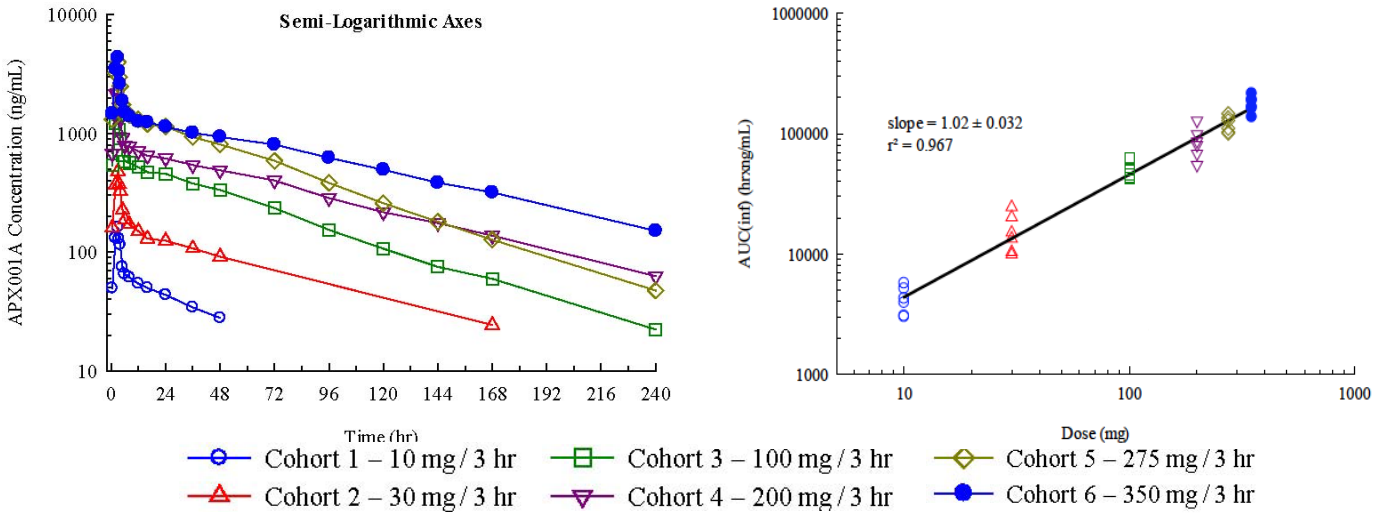
Study schematic



- Sentinel dosing was included in all cohorts
- The Safety Review Committee (◆SRC) evaluated sentinel subjects' safety data prior to continued dosing in each cohort
- The SRC evaluated safety and PK data prior to dose escalations

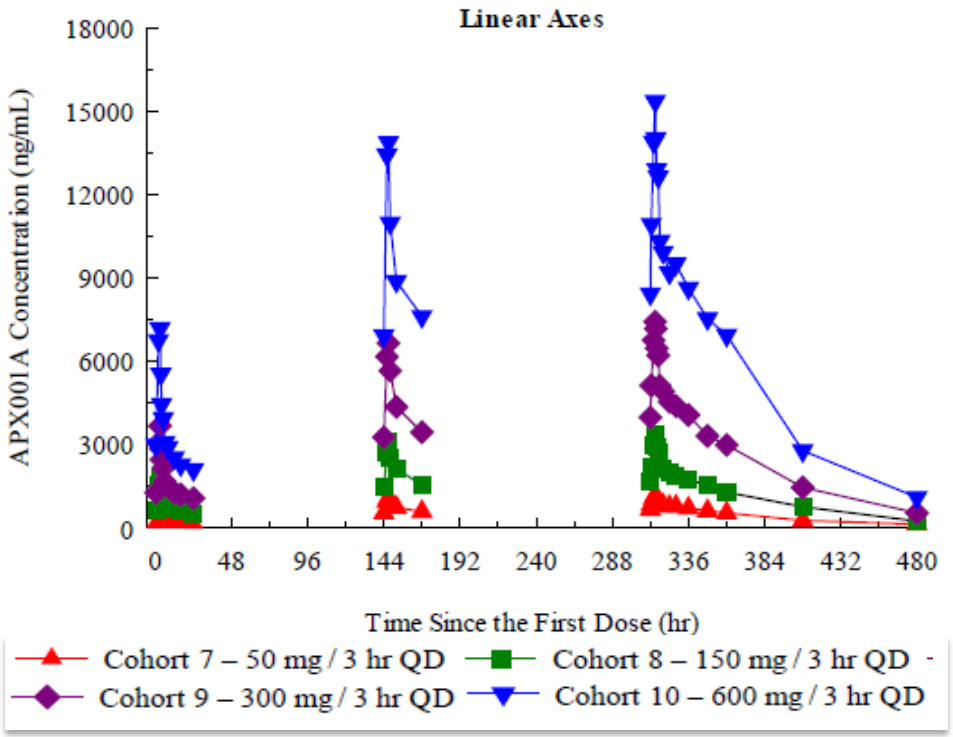
SAD 10-350 mg
MAD 50-600 mg od x 14d
SD 1000 mg
Load 1000 mg bid -> 600 mg od x7d

APX001-101 SAD IV PK



Dose (mg)	PK Parameters			
	C max (µg/mL)	AUC (0-24) (µg.hr/mL)	AUC (inf) (µg.hr/mL)	T ½ (hr)
10	0.16	1.54	4.05	39.2
30	0.48	4.33	14.13	50.8
100	1.44	14.36	50.37	52.5
200	2.41	20.75	83.17	67.0
275	3.96	37.07	119.74	48.6
350	4.33	38.17	173.42	74.9

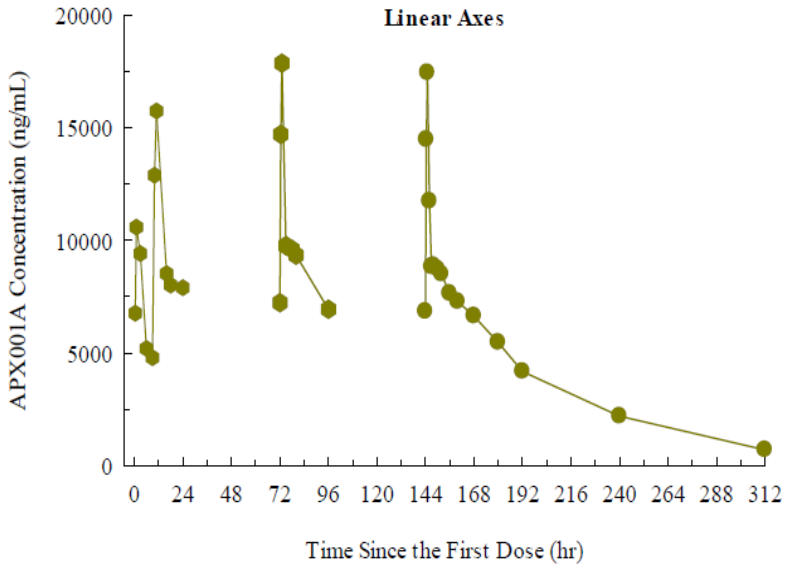
APX001-101 MAD IV PK



Cohort		PK Parameters		
		C max (µg/mL)	AUC (0-24) (µg.hr/mL)	T ½ (hr)
50 mg	Day 1	0.67	6.39	
	Day 7	1.09	17.57	
	Day 14	1.18	20.26	69.0
150 mg	Day 1	1.86	19.38	
	Day 7	3.09	48.68	
	Day 14	3.42	51.9	52.6
300 mg	Day 1	3.68	37.1	
	Day 7	6.65	104.1	
	Day 14	7.52	118.36	53.1
600 mg	Day 1	7.57	72.68	
	Day 7	14.5	217.1	
	Day 14	15.36	245.0	64.2

- 50, 150, 300 and 600 mg PO x 14 days
- $AUCs_{(0\text{-}24)}$ attain current targets for *Candida*, *Aspergillus*, *Fusarium*, *Scedosporium* and Mucorales

APX001-101 Loading Dose PK



Parameter*	1,000 mg / 2 hr at 0 & 9 hr Day 1	600 mg / 1 hr QD Day 4	600 mg / 1 hr QD Day 7
Cmax (ng/mL)	16,393 [24.7] (6)	17,863 [11.6] (5)	17,662 [9.14] (5)
Tmax (hr)	11.0 (6)	1.00 (5)	1.00 (5)
	[11.0 – 11.1]	[1.00 – 1.00]	[0.50 – 1.00]
AUC(0-24) (hr×ng/mL)	220,033 [20.4] (6)	219,458 [5.58] (5)	200,790 [13.3] (5)
λz (1/hr)	—†	—†	0.0145 [41.4] (4)
t½ (hr)	—†	—†	48.0 [41.4] (4)
CL	—†	—†	
(mL/hr)	—†	—†	2,286 [13.3] (5)
(mL/hr/kg)	—†	—†	33.4 [14.4] (5)
Vz	—†	—†	
(L)	—†	—†	162 [30.8] (4)
(L/kg)	—†	—†	2.27 [34.4] (4)

*Geometric mean [geometric %CV] (N) except Tmax for which the median (N) [Range] is reported.

- Target AUC for efficacy achieved on Day 1 using a well tolerated loading dose regimen
  - Day 1: 2 x 1000 mg, 2-hr infusion AM & PM
  - Day 2 to 7: 600 mg, 1-hr infusion AM only

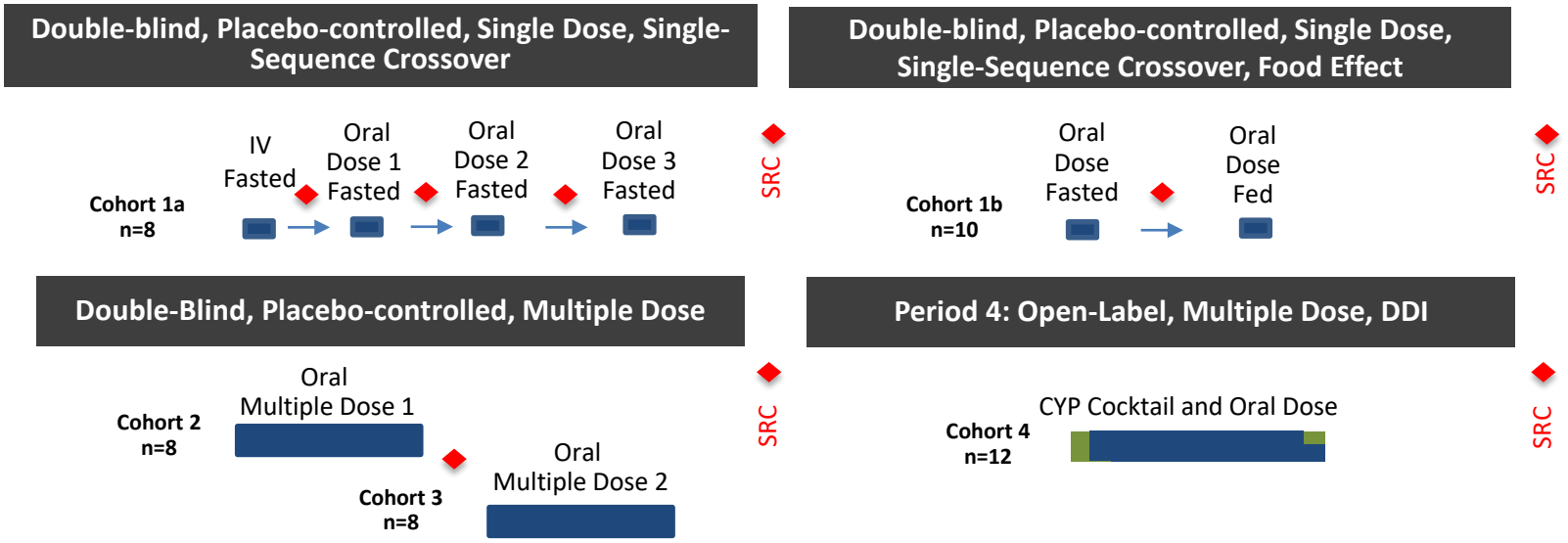
APX001-102 Oral Phase 1

Objectives

- Double-blind, placebo-controlled, randomized study in healthy volunteers
- Objectives included
  - evaluation of safety, tolerability, PK of single and multiple doses of APX001
  - Assessment of bioavailability of single doses of APX001 administered IV and orally
  - determine the effect of food on the PK of APX001 and APX001A following a single oral dose of administration APX001
  - evaluate the effect, if any, of APX001 on the PK of CYP isoenzyme substrates following repeated oral administration of APX001

APX001-102 Oral Phase 1

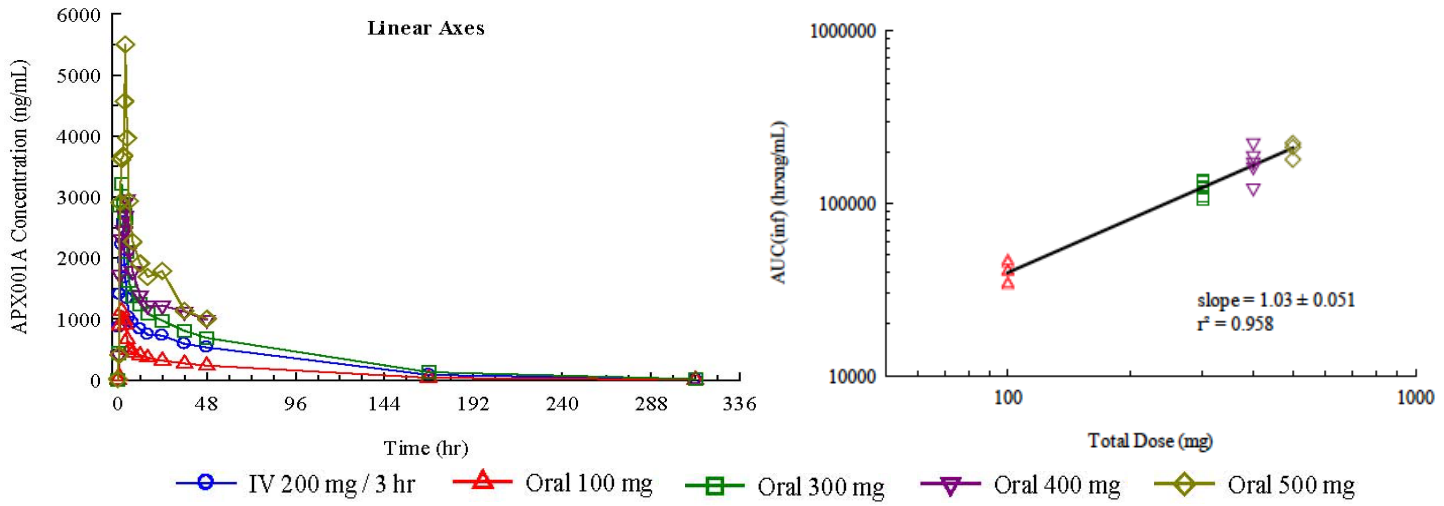
Study schematic



- Sentinel dosing was included in all cohorts
- The Safety Review Committee (◆SRC) evaluated sentinel subjects' safety data prior to continued dosing in each cohort
- The SRC evaluated safety and PK data prior to dose escalations

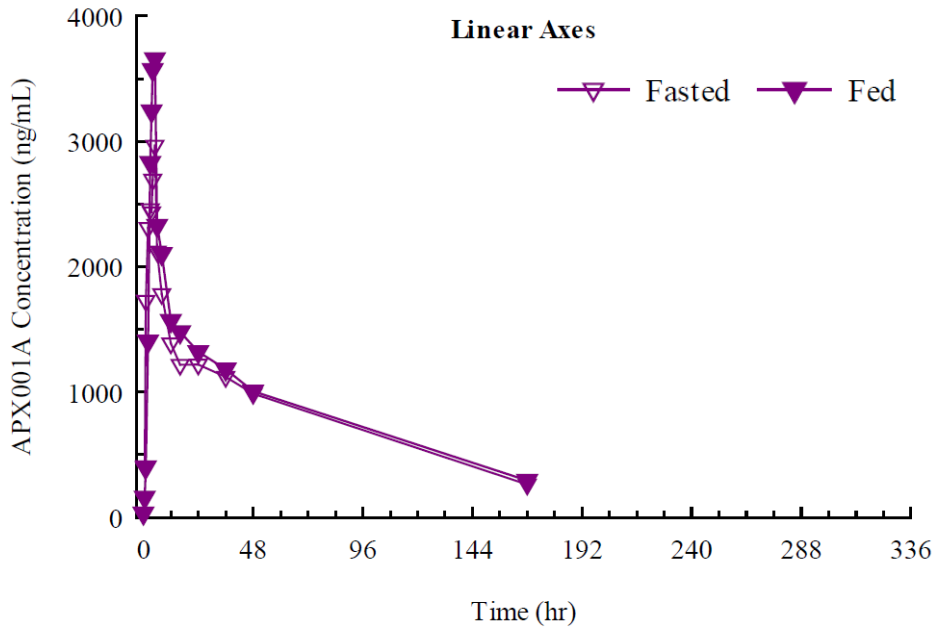
Cohort 1a 100-500 mg
Cohort 1b 400 mg
Cohort 2 and 3 MAD 500-1000 mg x14d
Cohort 4 500 mg x14d

APX001-102 SAD Oral PK



Dose (mg)	Administration Route	PK Parameters: APX001A					
		C-max (µg/mL)	AUC(0-24) (hr.µg/mL)	AUC(Inf)) (hr.µg/mL)	T ½ (hr)	T-max (hr)	F (%)
200	IV 3hr	2.64	18.47	87.53	49.1	3.0	-
100	PO	1.30	9.01	39.64	49.5	2.0	90.6
300	PO	3.75	27.36	122.23	52.5	2.5	93.1
400	PO	4.25	30.18	171.55	67.6	2.5	98.0
500	PO	6.53	43.65	204.30	49.9	3.0	93.4

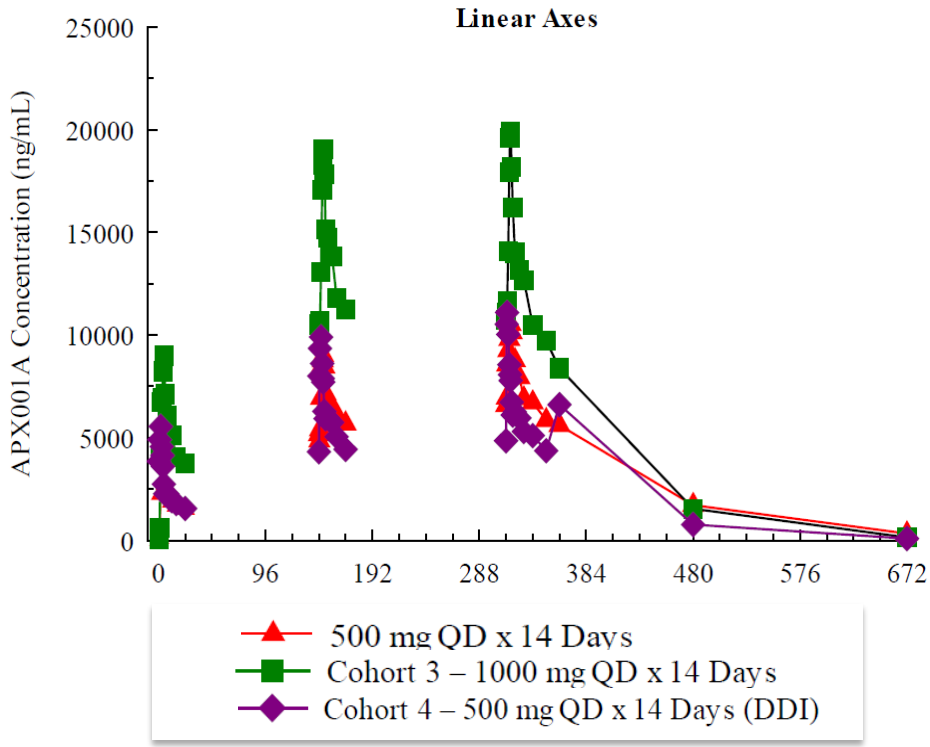
APX001-102 Oral Food Effect



Mean plasma concentrations 400 mg PO under fasted and fed conditions

Dose (mg)	Period	PK Parameters: APX001A					
		C-max (µg/mL)	AUC(0-24) (hr.µg/mL)	AUC(Inf)) (hr.µg/mL)	T ½ (hr)	T-max (hr)	F (%)
400	PO fasted	4.25	30.18	175.1	67.2	2.5	>90%
400	PO fed	4.52	32.33	190.0	67.6	3.78	>90%

APX001-102 MAD PO PK



Cohort		PK Parameters	
		C max (µg/mL)	AUC (0-24) (µg.hr/mL)
500 mg tablet	Day 1	6.17	50.73
	Day 7	10.87	154.46
	Day 14	11.95	192.38
500 mg solution	Day 1	5.85	56.71
	Day 7	10.42	139.96
	Day 14	12.42	152.55
1000 mg tablet	Day 1	10.59	118.82
	Day 7	21.33	315.56
	Day 14	21.27	325.84

- 500 mg, 1000 mg tablets and 500 mg oral solution x 14 days
- $AUCs_{(0\text{-}24)}$ attain current targets for *Candida, Aspergillus, Fusarium, Scedosporium* and Mucorales

Phase 1 – Safety Profile

- All single and multiple IV and oral doses of APX001 were well tolerated
  - Most were mild and did not require treatment
- Faster infusions (SD 0.5 hours and MD 1-hour) well tolerated
- Loading dose 1000 mg over 2-hr infusions twice daily well tolerated
- There were no severe AE or SAEs reported and there were no withdrawals due to treatment related AEs
- No AEs or laboratory safety tests results met any of the *a priori* rules that prevented dose escalation
- No DLTs were observed and the MTD was not determined/reached in these studies

Phase 1 - PK Profile

- Pharmacokinetic parameters are linear and dose proportional
- Low variability in PK parameters between patients
- Half-life ~2 days
- Oral bioavailability ~90%
- No food effect
- No clinically significant DDI data interactions
- Target exposures for efficacy against *Candida* and *Aspergillus* as well as the high MIC pathogens exceeded at doses that are safe and well tolerated
- After a single dose drug levels were above the MIC of *Candida* and *Aspergillus* for one week
- A twice daily loading dose achieves target exposure for efficacy against *Candida* and *Aspergillus* as well as the high MIC pathogens within 24 hours

APX001 - Summary

- Broad spectrum activity with IV & oral formulations
  - Once-daily first line monotherapy
  - Potential to treat all stages of infection (established, preemptive and prophylaxis)
- Excellent Phase 1 safety and PK profile
  - Target AUCs achieved with no clinically significant safety signals
- Conduct trials in high unmet medical need populations
  - Immunosuppressed patients with hematologic malignancies with invasive fungal infections
  - Resistant fungal pathogens
  - Populations where standard of care may not be appropriate