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2. SYNOPSIS

Study Title

A PHASE 1, OPEN-LABEL, FIXED-SEQUENCE, DRUG-DRUG INTERACTION STUDY OF APX001 TO EVALUATE THE EFFECTS OF CYP3A4 INHIBITION AND PAN-CYP INDUCTION IN TWO PARALLEL GROUPS OF HEALTHY MALE AND FEMALE SUBJECTS

Study Codes

Sponsor code : APX001-107
PRA code : AMY19558-19558X
EudraCT number : 2019-003586-17

Sponsor

Amplyx Pharmaceuticals, Inc., 12730 High Bluff Drive, Suite 160, San Diego, CA 92130, US
Sponsor's contact : Eric Ople, Manager, Clinical Operations

Contract Research Organization and Clinical Site

PRA-EDS, Van Swietenlaan 6, 9728 NZ Groningen, The Netherlands

Principal Investigator

Sjoerd van Marle, MD

Publication : None at time of writing this report

Study Period : Date of first screening to last follow-up: 16 Oct 2019 – 07 Mar 2020

Clinical Phase : Phase 1

Objectives

Cohort 1

Primary : To assess the effects of multiple doses of a cytochrome P450 (CYP)3A4 inhibitor, itraconazole (oral solution), on the pharmacokinetics (PK) of APX001 and APX001A, following intravenous (IV) administration of 500 mg APX001 (as a 3-hour infusion) twice daily (bid) for 1 day, with a dosing interval of approximately 9 hours.

Secondary : To assess the safety and tolerability of an IV dose (500 mg as a 3-hour infusion bid for 1 day, with a dosing interval of approximately 9 hours) of APX001 alone and when coadministered with itraconazole (oral solution).

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Cohort 2

Primary : To assess the effects of multiple doses of a pan-CYP inducer, oral rifampin, on the PK of APX001 and APX001A, following IV administration of 1000 mg APX001 (as a 3-hour infusion) bid for 1 day, with a dosing interval of approximately 9 hours.

Secondary : To assess the safety and tolerability of an IV dose (1000 mg as a 3-hour infusion bid for 1 day, with a dosing interval of approximately 9 hours) of APX001 alone and when coadministered with oral rifampin.

Design and Treatments

This was a Phase 1, open-label, fixed-sequence, drug-drug interaction (DDI) study of APX001 in healthy subjects. The study was performed in 2 parallel cohorts, to evaluate the effect of a CYP3A4 inhibitor, itraconazole (Cohort 1), and the effect of a pan-CYP inducer, rifampin (Cohort 2), on the PK of APX001 and APX001A.

The following treatments were administered:

Cohort 1

- Day 1: IV dose of 500 mg of APX001 in 3-hour infusion, bid, with a dosing interval of approximately 9 hours.
- Days 15 to 30: oral doses of 200 mg of itraconazole once daily (qd), under fasted conditions. On Days 15 to 17, subjects self-administered itraconazole at home.
- Day 18: IV dose of 500 mg of APX001 in 3-hour infusion in the morning (1.5 hours after dosing of itraconazole), repeated once in the evening after approximately 9 hours.

Cohort 2

- Day 1: IV dose of 1000 mg of APX001 in 3-hour infusion, bid, with a dosing interval of approximately 9 hours.
- Days 15 to 33: oral doses of 600 mg of rifampin qd, under fasted conditions. On Days 15 to 23, subjects self-administered rifampin at home.
- Day 24: IV dose of 1000 mg of APX001 in 3-hour infusion in the morning (1.5 hours after dosing of rifampin), repeated once in the evening after approximately 9 hours.

The study designs are shown in Figure S1 (Cohort 1) and Figure S2 (Cohort 2).

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Figure S1 Overview of Cohort 1 Study Design

Admission	APX001 Infusion 500 mg[a]		Discharge		Itraconazole 200 mg qd Oral Dosing at home	Admission	APX001 Infusion 500 mg[a] + Itraconazole 200 mg qd Oral Dosing[b]	Itraconazole 200 mg Oral Dosing	Discharge	→	Follow-up Visit
In-Clinic				Ambulatory[c]		In-Clinic					Ambulatory
D -1	D1	D1-D4	D4	D5-D14	D15-D17	D17	D18	D19-D30	D31		D38±1

bid=twice daily; D=Day; qd=once daily
[a] Infused over a 3-hour period bid.
[b] Administered qd, 1 hour before the start of breakfast and 1.5 hours before start of APX001 infusion.
[c] Ambulatory visits to the clinic on Days 6, 8, 10, 12, 14, 15, and 16

Figure S2 Overview of Cohort 2 Study Design

Admission	APX001 Infusion 1000 mg[a]		Discharge		Rifampin 600 mg qd Oral Dosing at home[b]	Admission	APX001 Infusion 1000 mg[a] + Rifampin 600 mg Oral Dosing[b]	Rifampin 600 mg qd Oral Dosing	Discharge	→	Follow-up Visit
In-Clinic				Ambulatory[c]		In-Clinic					Ambulatory
D -1	D1	D1-D4	D4	D5-D14	D15-D23	D23	D24	D25-D33	D34		D41±1

bid=twice daily; D=Day; qd=once daily
[a] Infused over a 3-hour period bid.
[b] Administered qd, 1 hour before the start of breakfast and 1.5 hours before the start of APX001 infusion.
[c] Ambulatory visits to the clinic on Days 6, 8, 10, 12, 14, 15, and 19

Study Schedule

Screening : Between Day -28 and Day -1 (admission)

Confinement period : <u>Cohort 1</u>
Two periods in the clinic from Day -1 (admission) up to Day 4 (morning), and from Day 17 up to Day 31 (morning). Between periods, subjects returned for ambulatory visits on Days 6, 8, 10, 12, 14, 15, and 16.
<u>Cohort 2</u>
Two periods in the clinic from Day -1 (admission) up to Day 4 (morning), and from Day 23 up to Day 34 (morning). Between periods, subjects returned for ambulatory visits on Days 6, 8, 10, 12, 14, 15, and 19.

Follow-up : Day 38±1 (Cohort 1) or Day 41±1 (Cohort 2), ie, 7±1 days after Discharge.

Subjects

Up to 36 subjects were planned to be enrolled in this study, to ensure 16 completers per cohort. Two subjects withdrew after randomization but before dosing, and were replaced. Thus, a total of 38 subjects were enrolled and randomized.

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Main Criteria for Inclusion

Age : 18 to 60 years, inclusive, at screening
Weight : ≥50 kg
Body mass index (BMI) : 18.0 to 32.0 kg/m^2, inclusive
Subjects : healthy male and/or female subjects

Study Drug

Investigational Medicinal Product

Active substance : APX001
Activity : Inhibition of the fungal enzyme glycosylphosphatidylinositol-anchored wall transfer protein 1 (GWT1)
Indication : Invasive fungal infections
Strength : 20 mg/mL (diluted in saline for IV infusion)
Dosage form : IV infusion
Manufacturer : Patheon API Services, Germany (APX001 drug substance for IV infusion); PRA Pharmacy NL manufactured the 20 mg/mL IV concentrate
Batch number : RH05L177AO

CYP3A4 Inhibitor

Active substance : Itraconazole
Activity : Azole antifungal
Strength : 10 mg/mL (20 mL; 200 mg)
Dosage form : Oral solution
Manufacturer : Sourced locally by PRA Pharmacy
Batch number : JBB6800

Pan-CYP Inducer

Active substance : Rifampin
Activity : Antibiotic
Strength : 300 mg (2 capsules for 600 mg dose)
Dosage form : Capsules
Manufacturer : Sourced locally by PRA Pharmacy
Batch number : 7G059A

Variables

Safety : Adverse events (AEs), clinical laboratory assessments (clinical chemistry, hematology, coagulation, and urinalysis), vital signs, 12-lead electrocardiograms (ECGs), and physical examinations.
PK : Blood samples were collected for the analysis of plasma concentrations of APX001 and APX001A at the time points indicated in the schedule of

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assessments. The following primary PK parameters were calculated, when possible, using standard noncompartmental methods: area under the plasma concentration-time curve (AUC) from time 0 to infinity (AUC_{0-inf}), AUC from time 0 to the time of the last measurable concentration (AUC_{0-t}), and maximum observed concentration (C_{max}). Additional parameters included time of maximum observed concentration (T_{max}), AUC from time 0 to 23 hours (AUC_{0-23}),apparent terminal elimination rate constant (λz), apparent terminal elimination half-life ($t_{1/2}$), total clearance (CL), and volume of distribution during the terminal phase (Vz).

: Blood samples were collected for the potential analysis of trough levels of itraconazole (Cohort 1) and rifampin (Cohort 2).

Statistical Methods

Sample size calculation : The primary objective of this study was to assess the effect of itraconazole and rifampin on the PK of APX001 and APX001A. For each cohort, 18 subjects were included to ensure 16 subjects completed all assessments. The number of subjects was chosen based on feasibility to evaluate PK, safety, and tolerability. This number of subjects was considered sufficient to meet the study objectives.

Safety parameters : AEs, clinical laboratory assessments, vital sign measurements, and 12-lead ECG assessments were tabulated and summarized by treatment, where possible, using descriptive methodology. Physical examination findings were listed. No formal statistical analyses were planned for the safety data.

PK parameters : Descriptive statistics (number, arithmetic mean, arithmetic SD, median, minimum, maximum, geometric mean, and geometric coefficient of variation [CV%]) were calculated, when possible, for plasma concentrations and PK parameters of APX001 and APX001A.

: The primary PK parameters were AUC_{0-inf}, AUC_{0-t}, and C_{max} for APX001A on the primary PK days indicated in the schedule of assessments. For AUC_{0-inf} and AUC_{0-t}, the integrated values including the morning and evening doses were taken; for C_{max} the primary PK parameter was the value observed after the second (evening) infusion on both APX001 dosing days. All other PK parameters were regarded as secondary and were not subjected to inferential statistical analysis. An Analysis of Variance (ANOVA) was used to analyze the natural log-transformed primary PK parameters with day as the fixed effect and subject as a random effect. Estimates of geometric mean ratios together with the corresponding 90% CIs were derived for the comparisons of the primary PK parameters for APX001A as follows:

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- Cohort 1: APX001 plus itraconazole (test; Day 18) versus APX001 alone (reference; Day 1).
- Cohort 2: APX001 plus rifampin (test; Day 24) versus APX001 alone (reference; Day 1).

: Descriptive statistics (number, arithmetic mean, arithmetic SD, median, minimum, maximum, geometric mean, and geometric CV%) were calculated, when possible, for plasma concentrations of itraconazole (Cohort 1).

Results

Subject Disposition

A total of 80 subjects were screened, and 38 of these subjects were included in the study. Two subjects were randomized but withdrew before dosing, and they were replaced by 2 reserve subjects. Four subjects withdrew during the course of the study. Thirty two (32) subjects completed the study as per protocol (Table S1).

Table S1 Summary of Subject Disposition

	Cohort 1 N=20 n (%)	Cohort 2 N=18 n (%)
Randomized	20 (100)	18 (100)
Dosed	18 (90.0)	18 (100)
Safety Analysis Set	18 (90.0)	18 (100)
PK Analysis Set	16 (80.0)	17 (94.4)
Completed Study	16 (80.0)	16 (88.9)
Discontinued Study	4 (20.0)	2 (11.1)
Reason for Discontinuation		
Withdrawal by Subject Before Dosing	2 (10.0)	
Adverse Event	1 (5.0)	
Due to Family Circumstances		1 (5.6)
Personal Reason	1 (5.0)	
Withdrawal by Subject		1 (5.6)

N=number of subjects per cohort; n=number of subjects; PK=pharmacokinetic(s)
Percentages (%) are based on the randomized set.

Demographics

In Cohort 1 a total of 12 male (66.7%) and 6 female subjects (33.3%) between 21 and 60 years of age, and with a BMI between 21.3 and 31.3 kg/m^2 were dosed in the study. A total of 16 subjects (88.9%) were of white race and 2 subjects (11.1%) were of multiple race (white + Asian). One subject (5.6%) was of Hispanic or Latino ethnicity.

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In Cohort 2 a total of 11 male (61.1%) and 7 female subjects (38.9%) between 26 and 60 years of age, and with a BMI between 19.0 and 31.8 kg/m^2 were dosed in the study. A total of 15 subjects (83.3%) were of white race, 2 subjects (11.1%) were of multiple race (white + Asian), and 1 subject (5.6%) was Asian. None of the 18 subjects were of Hispanic or Latino ethnicity.

On average, the cohorts were comparable with regard to the main demographic characteristics.

Safety

In this section only treatment-emergent AEs (TEAEs) will be discussed.

In total 30 subjects (83.3%) experienced at least 1 of a total of 188 TEAEs. The TEAEs were distributed across the 6 different treatments as follows:

Cohort 1

APX001	:	9 subjects (50.0%) experiencing 21 TEAEs
Itraconazole	:	1 subject (5.9%) experiencing 2 TEAEs
APX001 + itraconazole	:	9 subjects (52.9%) experiencing 20 TEAEs

Cohort 2

APX001	:	14 subjects (77.8%) experiencing 49 TEAEs
Rifampin	:	13 subjects (72.2%) experiencing 47 TEAEs
APX001 + rifampin	:	14 subjects (82.4%) experiencing 49 TEAEs

There were no deaths or other serious adverse events (SAEs) during this study. All TEAEs were transient and resolved or were resolving at follow-up. One subject in Cohort 1 withdrew due to anxiety of mild severity.

Severity

The majority of the 188 TEAEs were of mild severity, only 2 TEAEs experienced by 2 subjects (5.6%) were of moderate severity. The 2 TEAEs that were considered moderate were 1 event of elevated hepatic transaminases after treatment with itraconazole, and 1 event of headache. Neither was considered related to the study drug APX001. The increase in hepatic transaminases was considered related to itraconazole.

Relationship

Of the 188 TEAEs, 37 TEAEs reported by 12 subjects (33.3%) were considered related to the study drug APX001. The number of related events was higher in Cohort 2 compared to Cohort 1 (33 out of a total of 145 events and 4 out of a total of 43 events, respectively). The most frequently reported TEAEs that were considered related to the study drug as judged by the Principal Investigator were headache, nausea, and hot flushes.

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The Most Frequently Reported TEAEs (All TEAEs [APX001, and itraconazole or rifampin])
The most frequently reported TEAEs by system organ class (SOC) (reported by at least 20% of the subjects) were in decreasing order:

- General Disorders and Administration Site Conditions (55 TEAEs reported by 22 subjects [61.1%]).
- Nervous System Disorders (37 TEAEs reported by 16 subjects [44.4%]).
- Gastrointestinal Disorders (30 TEAEs reported by 10 subjects [27.8%]).
- Respiratory, Thoracic, and Mediastinal Disorders (13 TEAEs reported by 10 subjects [27.8%]).
- Renal and Urinary Disorders (10 TEAEs reported by 8 subjects [22.2%]).

The percentages of subjects reporting TEAEs in the SOC of General Disorders and Administration Site Conditions were highest in Cohort 1 after the 500 mg APX001 (bid) dose on Day 18 + itraconazole on Days 18 to 30, and in Cohort 2 after the 1000 mg APX001 (bid) dose on Day 1, and after the 1000 mg APX001 (bid) dose on Day 24 + rifampin on Days 24 to 33. The percentages of subjects reporting TEAEs in the SOC of Nervous System Disorders, Gastrointestinal Disorders, and Renal and Urinary Disorders were higher in Cohort 2 than in Cohort 1.

The most frequently reported TEAEs by preferred term (PT) (reported by at least 15% of the subjects) were in decreasing order:

- Headache (18 TEAEs reported by 10 subjects [27.8%])
- Chromaturia (8 TEAEs reported by 8 subjects [22.2%])
- Fatigue (8 TEAEs reported by 7 subjects [19.4%])
- Catheter site irritation (10 TEAEs reported by 6 subjects [16.7%])
- Infusion site irritation (6 TEAEs reported by 6 subjects [16.7%])
- Hot Flush (6 TEAEs reported by 6 subjects [16.7%])

The percentages of subjects reporting headache, fatigue, catheter site irritation, infusion site irritation, and hot flush were higher in Cohort 2 than in Cohort 1. Chromaturia, a known AE of rifampin, occurred only during rifampin administration.

One subject experienced clinically significant increased levels of the liver enzymes alanine aminotransferase (ALT) up to ~8× the upper limit of normal (ULN), aspartate aminotransferase (AST) up to ~11× ULN, and lactate dehydrogenase (LDH) up to ~ 2× ULN, starting on Day 30, lasting up to Day 84, which was considered to be related to itraconazole.
With regard to clinical laboratory findings, vital signs, ECG, body weight, and physical examination, no trends or clinically relevant changes were observed, with the exception of 1 subject showing clinically significant increases in liver enzyme levels, as described above.

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Pharmacokinetics

Itraconazole DDI (Cohort 1)

APX001

The geometric mean values for C_{max}, AUC_{0-t}, and AUC_{inf} of APX001 were essentially the same with and without treatment with itraconazole (Table S2) and the least squares geometric mean ratios (LSGMRs) ranged from 95.06% to 99.74% with associated 90% CIs within 80.00% to 125.00% (Table S3), indicating no effect of CYP3A4 inhibition on exposure to APX001. This is not unexpected since APX001 is not a CYP3A4 substrate.

Table S2 Summary of PK Parameters for APX001 After IV Administration of 2 Doses of 500 mg of APX001 Over 3 Hours at 9 Hour Intervals Alone and Concomitant With Administration of Itraconazole 200 mg QD × 16 Days

Parameter*	APX001 Alone	APX001 + Itraconazole
Cmax (ng/mL)	1,520 (18.6) [16]	1,516 (15.1) [16]
Tmax (hr)	10.5 [16]	6.53 [16]
	(0.50 – 12.0)	(0.50 – 12.0)
AUC(0-23) (hr×ng/mL)	9,945 (16.5) [16]	9,454 (18.2) [16]
AUC(0-t) (hr×ng/mL)	9,945 (16.5) [16]	9,454 (18.2) [16]
AUC(inf) (hr×ng/mL)	10,191 (18.3) [12]	9,454 (18.2) [16]
λz (1/hr)	1.83 (14.4) [12]	1.76 (31.0) [16]
t½ (hr)	0.38 (14.4) [12]	0.39 (31.0) [16]
CL (mL/hr)	98,128 (18.3) [12]	105,770 (18.2) [16]
Vz (L)	53.6 (22.5) [12]	60.1 (33.7) [16]

hr=hour; IV=intravenous; PK=pharmacokinetic(s); qd=once daily

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

Table S3 Statistical Comparison of PK Parameters for APX001 After IV Administration of 2 Doses of 500 mg of APX001 Over 3 hours at 9 Hour Intervals Alone and Concomitant with Administration of Itraconazole 200 mg QD × 16 days

	Least Squares Geometric Means		Geometric Mean Ratio (%)		Within Subject
Parameter	APX001 + Itraconazole	APX001 Alone	Estimate	90% Confidence Interval	CV (%)
Cmax	1,515.80	1,519.76	99.74	94.62 → 105.14	8.52
AUC(0-t)	9,453.89	9,945.16	95.06	88.62 → 101.96	11.35
AUC(inf)	9,454.49	9,717.11	97.30	91.01 → 104.02	9.13

IV=intravenous; PK=pharmacokinetic(s); qd=once daily

Based on analysis of natural log-transformed data.

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APX001A

The geometric mean values for C_{max}, AUC_{0-t}, and AUC_{inf} of APX001A were essentially the same with and without treatment with itraconazole (Table S4) and the LSGMRs ranged from 98.25% to 101.83% with associated 90% CIs within 80.00% to 125.00% (Table S5), indicating no effect of CYP3A4 inhibition on exposure to APX001A.

Table S4 Summary of PK Parameters for APX001A After IV Administration of 2 Doses of 500 mg of APX001 Over 3 Hours at 9 Hour Intervals Alone and Concomitant With Administration of Itraconazole 200 mg QD × 16 Days.

Parameter*	APX001 Alone	APX001 + Itraconazole
Cmax (ng/mL)	6,936 (23.2) [16]	7,063 (19.4) [16]
Tmax (hr)	12.0 [16]	12.0 [16]
	(2.98 – 12.5)	(11.0 – 12.2)
AUC(0-23) (hr×ng/mL)	83,663 (23.2) [16]	83,458 (21.2) [16]
AUC(0-t) (hr×ng/mL)	428,571 (19.9) [16]	421,057 (21.0) [16]
AUC(inf) (hr×ng/mL)	460,142 (21.3) [16]	458,447 (23.6) [16]
λz (1/hr)	0.0090 (25.4) [16]	0.0085 (28.2) [16]
t½ (hr)	77.3 (25.4) [16]	81.1 (28.2) [16]
CL (mL/hr)	1,663 (21.3) [16]	1,669 (23.6) [16]
Vz (L)	185 (25.1) [16]	195 (22.4) [16]

hr=hour; IV=intravenous; PK=pharmacokinetic(s); qd=once daily
*Geometric mean [geometric %CV] (N) except for Tlag and Tmax for which the median (N) [Range] is reported.

Table S5 Statistical Comparison of PK Parameters for APX001A After IV Administration of 2 Doses of 500 mg of APX001 Over 3 Hours at 9 Hour Intervals Alone and Concomitant With Administration of Itraconazole 200 mg QD × 16 Days.

	Least Squares Geometric Means		Geometric Mean Ratio (%)		Within Subject
Parameter	APX001 + Itraconazole	APX001 Alone	Estimate	90% Confidence Interval	CV (%)
Cmax	7,063.21	6,936.12	101.83	97.00 → 106.91	7.86
AUC(0-t)	421,057.07	428,570.72	98.25	95.26 → 101.33	4.98
AUC(inf)	458,464.08	460,151.04	99.63	95.76 → 103.67	6.41

IV=intravenous; PK=pharmacokinetic(s); qd=once daily
Based on analysis of natural log-transformed data.

All subjects had predose concentrations of itraconazole on Days 19, 25, and 31 that were ≥ LLOQ (0.5 ng/mL). Consistent with the known PK of itraconazole, the geometric means increased from 308 ng/mL on Day 19 to 943 ng/mL on Day 31. The data demonstrated that all subjects were exposed to itraconazole and validate the conclusion of no effect of CYP3A4 inhibition on exposure to APX001A.

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Rifampin DDI (Cohort 2)

APX001

The geometric mean values for C_{max}, AUC_{0-t}, and AUC_{inf} of APX001 were comparable with and without treatment with rifampin (Table S6). The LSGMRs ranged from 114.16% to 116.54% with associated 90% CIs for the AUCs within 80.00% to 125.00% and the upper limit for the 90% CI for C_{max} slightly above 125.00% (Table S7) — overall, this indicates no effect of pan-CYP induction on exposure to APX001. This is not unexpected since APX001 is not a CYP substrate.

Table S6 Summary of PK Parameters for APX001 After IV Administration of 2 Doses of 1000 mg of APX001 Over 3 Hours at 9 Hour Intervals Alone and Concomitant With Administration of Rifampin 600 mg QD × 19 days

Parameter*	APX001 Alone	APX001 + Rifampin
Cmax (ng/mL)	2,974 (24.2) [17]	3,395 (39.7) [17]
Tmax (hr)	9.50 [17]	11.0 [17]
	(0.50 – 12.1)	(0.50 – 12.0)
AUC(0-23) (hr×ng/mL)	18,162 (22.3) [17]	21,166 (27.6) [17]
AUC(0-t) (hr×ng/mL)	18,162 (22.3) [17]	21,166 (27.6) [17]
AUC(inf) (hr×ng/mL)	18,163 (22.3) [17]	21,167 (27.6) [17]
λz (1/hr)	1.59 (18.4) [17]	1.68 (21.2) [17]
t½ (hr)	0.44 (18.4) [17]	0.41 (21.2) [17]
CL (mL/hr)	110,117 (22.3) [17]	94,488 (27.6) [17]
Vz (L)	69.4 (30.4) [17]	56.4 (29.8) [17]

hr=hour; IV=intravenous; PK=pharmacokinetic(s); qd=once daily

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

Table S7 Statistical Comparison of PK Parameters for APX001 After IV Administration of 2 Doses of 1000 mg of APX001 Over 3 Hours at 9 Hour Intervals Alone and Concomitant With Administration of Rifampin 600 mg QD × 19 Days

	Least Squares Geometric Means		Geometric Mean Ratio (%)		Within Subject
Parameter	APX001 + Rifampin	APX001 Alone	Estimate	90% Confidence Interval	CV (%)
Cmax	3,395.08	2,974.05	114.16	100.67 → 129.45	21.23
AUC(0-t)	21,165.88	18,161.89	116.54	109.67 → 123.84	10.17
AUC(inf)	21,166.63	18,162.57	116.54	109.67 → 123.84	10.17

IV=intravenous; PK=pharmacokinetic(s); qd=once daily

Based on analysis of natural log-transformed data.

APX001A

The geometric mean value for C_{max} of APX001A was slightly lower after administration of rifampin, 12,112 ng/mL vs. 13,897 ng/mL (Table S8) with a LSGMR of 87.16% and associated 90% CI of 83.14% to 91.37% (Table S9), demonstrating no significant effect. However, AUC_{0-t}, and AUC_{inf} were reduced after

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pan-CYP induction by rifampin (Table S8), with LSGMRs of 56.43% and 54.72%, respectively, and associated 90% CIs well below the 80.00% to 125.00% no effect window (Table S9). This demonstrates that the overall exposure to APX001A is significantly reduced by pan-CYP induction.

Table S8 Summary of PK Parameters for APX001A After IV Administration of 2 Doses of 1000 mg of APX001 Over 3 hours at 9 Hour Intervals Alone and Concomitant With Administration of Rifampin 600 mg QD × 19 Days

Parameter*	APX001 Alone	APX001 + Rifampin
Cmax (ng/mL)	13,897 (31.0) [17]	12,112 (31.8) [17]
Tmax (hr)	12.0 [17]	12.0 [17]
	(2.98 – 12.5)	(2.98 – 12.1)
AUC(0-23) (hr×ng/mL)	165,095 (32.6) [17]	142,083 (31.1) [17]
AUC(0-t) (hr×ng/mL)	772,242 (19.2) [17]	435,791 (23.6) [17]
AUC(inf) (hr×ng/mL)	821,908 (18.5) [17]	449,723 (23.8) [17]
λz (1/hr)	0.0098 (36.1) [17]	0.0166 (33.6) [17]
t½ (hr)	70.7 (36.1) [17]	41.7 (33.6) [17]
CL (mL/hr)	1,862 (18.5) [17]	3,403 (23.8) [17]
Vz (L)	190 (40.8) [17]	205 (42.4) [17]

hr=hour; IV=intravenous; PK=pharmacokinetic(s); qd=once daily
*Geometric mean [geometric %CV] (N) except for Tlag and Tmax for which the median (N) [Range] is reported.

Table S9 Statistical Comparison of PK Parameters for APX001A After IV Administration of 2 Doses of 1000 mg of APX001 Over 3 Hours at 9 Hour Intervals Alone and Concomitant With Administration of Rifampin 600 mg QD × 19 Days

	Least Squares Geometric Means		Geometric Mean Ratio (%)		Within Subject
Parameter	APX001 + Rifampin	APX001 Alone	Estimate	90% Confidence Interval	CV (%)
Cmax	12,112.38	13,897.27	87.16	83.14 → 91.37	7.90
AUC(0-t)	435,791.19	772,242.49	56.43	53.97 → 59.00	7.45
AUC(inf)	449,722.78	821,907.66	54.72	52.26 → 57.29	7.69

IV=intravenous; PK=pharmacokinetic(s); qd=once daily
Based on analysis of natural log-transformed data.

Conclusions

Safety

- Treatment with an IV dose of 500 mg of APX001 over 3 hours bid, alone (Day 1), oral doses of 200 mg itraconazole qd Day 15 to Day 30, and 500 mg of IV APX001 over 3 hours bid coadministered with an oral dose of 200 mg itraconazole qd (Day 18) was safe and well tolerated.

Name of Sponsor/Company: Amplyx Pharmaceuticals Inc.	**Individual Study Table Referring to Part .. of the Dossier**		**(For National Authority Use Only)**
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- Treatment with an IV dose of 1000 mg of APX001 over 3 hours bid, alone (Day 1), oral doses of 600 mg rifampin qd Day 15 to Day 33, and 1000 mg of IV APX001 over 3 hours bid coadministered with an oral dose of 600 mg rifampin qd (Day 24) was safe and well tolerated.
- The number of TEAEs, the percentage of subjects experiencing TEAEs, and the number of TEAEs reported as possibly related to study drug were higher after the 1000 mg of IV APX001 bid infusion compared to the 500 mg of IV APX001 bid infusion.
- The most frequently reported TEAEs by PT were headache, chromaturia (only during rifampin administration), fatigue, catheter site irritation, infusion site irritation, and hot flushes. The percentage of subjects experiencing these TEAEs was higher in Cohort 2.
- Coadministration of APX001 with itraconazole or rifampin did not affect safety and tolerability compared to administration of APX001 alone.
- One subject withdrew from the study due to a TEAE (mild anxiety, not related to APX001) that occurred after administration of APX001+ itraconazole.
- There were no deaths or SAEs reported during the study.
- With respect to clinical laboratory findings, 1 subject showed increased levels of hepatic transaminases AST (up to ~11× ULN), and ALT (up to ~8× ULN) from Day 30 until Day 77 (AST) and Day 84 (ALT), which were considered related to itraconazole. There were no concomitant elevations in bilirubin.
- There were no other clinically significant findings with respect to clinical laboratory, vital signs, ECG, or physical examination.

<u>Pharmacokinetics</u>

- Administration of APX001 after treatment with itraconazole, a strong CYP3A4 inhibitor, had no effect on the exposure to either the prodrug, APX001, or to the active moiety, APX001A, as measured by C_{max}, AUC_{0-t}, and AUC_{inf}.
- Administration of APX001 after treatment with rifampin, a strong pan-CYP inducer, had no effect on the exposure to APX001, a non-CYP substrate. Although there was no significant change in the geometric mean C_{max} for APX001A, there was an approximate 45% decrease in the extent of APX001A exposure as measured by AUC_{0-t} and AUC_{inf}.