

Dose Escalation, Safety, Tolerability and Pharmacokinetics of a Novel HIV-1 NNRTI, IDX899 in Healthy Subjects

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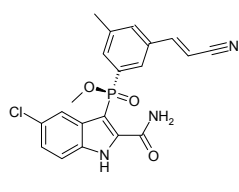
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Background

- Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are valuable components of antiretroviral combination therapy for the treatment of human immunodeficiency virus type 1 (HIV-1)-infection.
- IDX899 (see Figure 1) is a novel NNRTI drug candidate for the treatment of HIV-1 infection with potent *in vitro* antiviral characteristics and a higher barrier to resistance to efavirenz (EFV).¹
- In these Phase I trials, we investigated the safety and pharmacokinetic (PK) profile of IDX899 following single escalating and multiple doses of IDX899 in healthy volunteers.

Figure 1. Structure of IDX899



Objectives

- To evaluate the safety and tolerability of escalating single or multiple doses of IDX899 following oral administration in healthy subjects.
- To evaluate pharmacokinetics of single and multiple doses of IDX899.
- To determine food and gender effect on the pharmacokinetics of IDX899.

Methods

Subjects

- The NV-05A-001 trial was a Phase I dose-escalation study that enrolled 76 healthy adult male subjects (56 and 20 for the single dose and repeat dose steps, respectively) and nine female subjects of non-childbearing potential.

Dosing Schedule

- Single-dose escalation** - Male subjects (8/dose) were randomized 6:2 ratio to IDX899 or matching placebo to the following single escalating dose cohorts: 50 (fasted), 100 (fasted), 200 (fasted/fed), 400 (fasted/fed), 800 (fed) or 1200 (fed) mg.
- Food effect** - During single dose escalation, male subjects randomized to the 200 mg fast cohort received, after a 7-day washout period, an additional dose of 200 mg under fed conditions to assess food effect.
- An additional cohort of male subjects received a single dose of 400 mg under fed conditions to confirm food effect observed at 200 mg.
- Gender effect** - A cohort of non-childbearing healthy females was enrolled and received a single 400 mg dose under fed conditions to assess potential gender difference.
- Multiple doses** - After the completion of single dose escalation, two cohorts of male subjects (10/cohort randomized 8:2 active to placebo ratio) were enrolled and received repeat doses of 800 QD or 400 mg BID for 7 days under fed conditions.

PK Sampling and Analysis

- Serial plasma samples were obtained after dosing and quantitated for IDX899 using a validated LC/MS-MS methodology.
- PK parameters, obtained using standard non-compartmental analysis, include C_{max} , T_{max} , $AUC_{0-\infty}$, C_{24h}/C_{min} , and $T_{1/2}$. Mean \pm SD [Median (Range)] for T_{max} are presented.

Methods (cont'd)

Safety Analysis

- Safety measurements included clinical history, laboratory evaluations, physical examination, vital signs, and adverse event (AE) assessments.

Drug-Drug Interaction Studies

- Drug-drug interaction studies with Truvada[®] (emtricitabine and tenofovir disoproxil fumarate) and Reyataz[®] (atazanavir, ATV) are completed and analyses are in progress. Results from a preliminary analysis are presented for the IDX899/ATV study.

Results

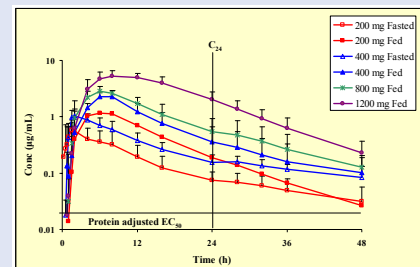
Demographics

Table 1. Demographic Characteristics of Subjects

Parameter	Statistic	Single Dose		Multiple Dose		
		Placebo (N=16)	Active (N=49)	Placebo (N=4)	Active (N=16)	
Age (years)	Mean (SE)	30.8 (2.60)	33.8 (1.76)	28.3 (1.97)	31.2 (2.43)	
Weight (kg)	Mean (SE)	75.3 (2.43)	77.1 (1.35)	76.4 (1.86)	76.8 (2.94)	
Height (cm)	Mean (SE)	172.3 (1.88)	174.5 (1.17)	168.8 (3.15)	173.1 (2.03)	
Gender	n (%)					
	Male	14 (87.5)	42 (85.7)	4 (100.0)	16 (100.0)	
	Female	2 (12.5)	7 (14.3)	0	0	
Race	n (%)					
	White	14 (87.5)	39 (79.6)	4 (100.0)	12 (75.0)	
	Black or African American	2 (12.5)	8 (16.3)	0	4 (25.0)	
	Asian	0	1 (2.0)	0	0	
	American Indian or Alaska Native	0	1 (2.0)	0	0	
	Hispanic or Latino	n (%)	6 (37.5)	8 (16.3)	2 (50.0)	7 (43.8)
	Not Hispanic or Latino	n (%)	10 (62.5)	41 (83.7)	2 (50.0)	9 (56.3)

Pharmacokinetics

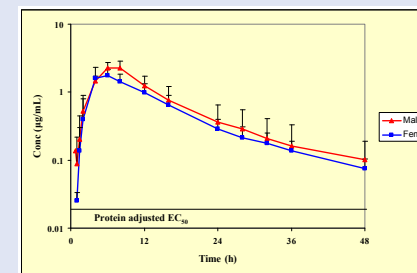
Figure 2: Concentration-Time Profiles of IDX899 Following Single Dose Administration in Male Subjects



Results (cont'd)

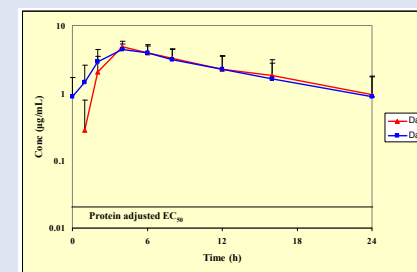
- Dose-proportional PK was observed in the 200 mg to 1200 mg dose range under fed conditions.
- Administration of IDX899 with a high-fat/high-calorie meal enhanced exposure by a factor of ~2 fold.
- Concentrations 24 h after single doses of 200-1200 mg exceeded the *in vitro* protein-binding adjusted EC_{50} (0.023 µg/mL) of IDX899 by approximately 10 to 40 fold. Steady-state trough concentrations exceed EC_{50} by approximately 40 to 90 fold.

Figure 3: Concentration-Time Profiles of IDX899 Following a Single 400 mg Dose



- Exposure to IDX899 in female and male subjects was comparable.

Figure 4: Concentration-Time Profiles of IDX899 Following 800 mg QD Administration



- Data show no evidence of accumulation or induction for IDX899 between Day 1 and Day 7.

Table 2. IDX899 Single Dose Pharmacokinetics Parameters

Dose (mg)	Condition	Sex	C_{max} (µg/mL)	T_{max} (h)	$AUC_{0-\infty}$ (µg/mL·h)	C_{24h} (µg/mL)	$T_{1/2}$ (h)
200	Fasted	M	0.67±0.18	1.5 (0.8-2.0)	7.1±4.1	0.074±0.030	11.9±3.1
	Fed	M	1.29±0.39	7.0 (4.0-8.1)	16.8±7.8	0.19±0.15	9.5±4.0
400	Fasted	M	1.08±0.21	1.8 (1.5-4.0)	14.7±3.9	0.16±0.055	14.6±2.5
	Fed	M	2.35±0.54	7.0 (6.0-8.2)	36.0±14.5	0.36±0.29	9.8±3.8
	Fed	F	1.88±0.44	5.0 (4.0-6.0)	26.5±7.1	0.29±0.12	13.9±6.1
800	Fed	M	3.04±0.37	6.0 (2.0-8.0)	47.2±12.1	0.55±0.39	11.5±2.2
	Fed	M	5.60±1.09	10.0 (6.0-12.0)	106.4±27.1	2.02±0.75	7.9±2.6

Table 3. IDX899 Multiple Dose Pharmacokinetics Parameters in Male Subjects under Fed Conditions

Dose (mg)	Regimen	C_{max} (µg/mL)	T_{max} (h)	$AUC_{0-\infty}$ (µg/mL·h)	C_{min} (µg/mL)
400 BID	Day 1	1.99±0.57	4.0 (4.0-4.0)	13.5±3.5	0.81±0.45
	Day 7	3.96±1.87	4.0 (4.0-6.0)	35.2±21.2	2.07±1.62
800 QD	Day 1	4.87±1.02	4.0 (4.0-6.0)	53.3±22.0	0.94±0.83
	Day 7	4.60±1.00	4.0 (4.0-6.0)	54.6±26.5	0.89±0.84

Safety

- There were no serious adverse events reported.
- The most common AEs reported across both single and multiple dose groups were headache (N=5/65), nausea (N=2/65), polyuria (2/65) and abnormal (vivid) dreams (N=2/65). All AEs were mild in intensity with exception of one event of moderate vomiting, in a female subject after a single dose of 400 mg IDX899, which resulted in discontinuation from the study. A second subject, a male in the multiple dose 800 mg group, discontinued for mild pruritus and urticaria which resolved within 26 hours after receiving diphenhydramine.

Table 4. Summary of Adverse Events (Single and Multiple Dose) observed in >1 subject

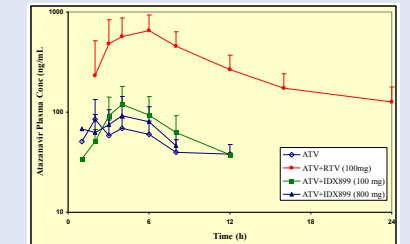
	Single Dose Placebo (N=16) n(%)	Single Dose Active (N=49) n(%)	Multiple Dose Placebo (N=4) n(%)	Multiple Dose Active (N=16) n(%)
Subject with any AEs	3 (18.8)	11 (22.4)	1 (25.0)	7 (43.8)
Abnormal Dreams	0	1 (2.0)	0	1 (6.3)
Dizziness	1 (6.3)	1 (2.0)	0	0
Headache	1 (6.3)	4 (8.2)	0	1 (6.3)
Nausea	1 (6.3)	2 (4.1)	0	0
Polyuria	0	0	0	2 (12.5)

Note: A subject with multiple AE occurrences under one treatment is counted only once in the AE category. Note: Subjects in the 200 mg single dose cohort received 200 mg under both fasted and fed conditions. Therefore, 200 mg fasted and fed subjects are counted once for overall N.

IDX899-Atazanavir Drug-Drug Interaction Study

- This study evaluated the PK interaction potential between ATV and IDX899 in comparison to the RTV-boosted ATV PK in healthy subjects. The single-dose PK of ATV alone, IDX899 alone and the two study drugs in combination was studied in two treatment groups administered respective doses of 100 mg and 800 mg IDX899. RTV-boosted ATV was used as positive control.
- A total of 18 healthy male or female (non-childbearing potential) subjects were enrolled and randomly assigned to one of the above three treatment groups.
- Plasma exposure of ATV was not markedly altered by IDX899.

Figure 5: Pharmacokinetic profiles of ATV (100 mg) alone or when combined with IDX899 or ritonavir (RTV)



Conclusions & Discussion

- Administered orally, IDX899 appears to be safe and well tolerated at single doses up to 1200 mg and multiple doses up to 800 mg QD over seven days in healthy subjects.
- Food enhanced absorption of IDX899; no gender effect was observed.
- No SAEs and no discernable pattern to laboratory abnormalities were observed.
- When combined with atazanavir, IDX899 did not markedly alter atazanavir pharmacokinetic parameters.
- IDX899 is currently in a proof of concept study in HIV-1 infected patients.

Acknowledgments

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Disclosures

D. Mayers, D Damphousse, J Sullivan-Bolyai, B Belanger and XJ Zhou are current employees and M Hard and B Fielman are former employees of Idenix Pharmaceuticals Inc.

References

- Richman DD, Jakubik J, Chapron C, et al (2008). 15th Conference on Retroviruses and Opportunistic Infections (CROI), Boston, USA.