IDX184, A Liver-Targeted Nucleotide HCV Polymerase Inhibitor: Results of a First-in-Man Safety and Pharmacokinetic Study

X.J. Zhou, K. Pietropaolo, J. Sullivan-Bólyai, B. Kuca, W. Liu, L. Xu, B. Belanger, S. Khan and D. Mayers
Idenix Pharmaceuticals, Inc., Cambridge, MA, USA

Email: zhou.xj@idenix.com

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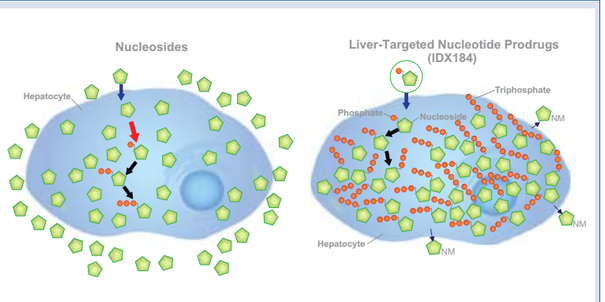
BACKGROUND

- The safety and antiviral activity of investigational, first generation nucleoside analog inhibitors of HCV NS5B may be limited by wide systemic distribution and inefficient conversion to the monophosphate, which limits production of active triphosphate (TP) species in the liver.
- As previously reported, IDX184 is a liver-targeted nucleotide prodrug designed to enhance formation of its active TP in the liver, while minimizing systemic exposure to the parent drug and the nucleoside metabolite (NM). See **Figure 1**.
- IDX184 is a potent and selective inhibitor of HCV *in vitro* and demonstrated multilog viral load reductions in HCV-infected chimpanzees receiving 10 mg/kg for 4 days.[1,2]

Figure 1: Metabolism of Nucleosides Versus Liver-Targeted Nucleotide Prodrugs Toward Formation of Nucleoside (●) Triphosphate (▬) Within Hepatocytes



OBJECTIVES

- To evaluate the safety and tolerability of IDX184 at single oral doses from 5 to 100 mg in healthy adult male and female subjects.
- To evaluate the plasma and urine PK of IDX184 and the NM at single oral doses.
- To guide dose selection for subsequent Phase Ib/IIa studies in HCV-infected patients.

METHODS

Subjects and Study Design

- Randomized, blinded, placebo-controlled, sequential cohort, single-dose escalation study
- Healthy male and female volunteers (N=48) between 19 and 65 years participated in this study.
- Eight subjects per dose were randomized 6:2 to a single dose of IDX184 (5, 10, 25, 50, 75 or 100 mg) or matching placebo. Subjects observed a fasting period of approximately 10 hr prior to dosing and an additional 4 hr post dosing.
- Safety data were reviewed at the end of each dosing cohort, prior to escalating to the next sequential dose.

PK Sampling and Analysis

- Plasma and urine PK of IDX184 and the NM were evaluated prior to dosing on Day 1 through a period of 120 hr (Day 6).
- Plasma and urine concentrations of IDX184 and the NM were quantified using validated LC/MS-MS methodologies.
- Plasma PK parameters, obtained using standard non-compartmental analysis, include C_{max}, T_{max}, AUC, $T_{1/2}$ and C_{24h}. Urine PK parameters include $Au_{0\text{-}t}$, % dose excreted and renal clearance (CL_R).

Statistical Analysis

- Summary statistics were used for PK parameters.
- Dose proportionality was assessed with respect to drug exposure parameters (AUC and C_{max}) by fitting a regression line and was to be concluded if the 95% CI for the regression slope contained 1.0 and was contained within the range 0.70, 1.30.

Safety Analysis

- Safety measurements included clinical history, routine laboratory evaluations, physical examination, 12-lead ECGs, vital signs and adverse event (AE) assessments.

RESULTS

Demographics

Table 1: Demographic Characteristics of Subjects

Parameter	Placebo N=12	5 mg N=6	10 mg N=6	25 mg N=6	50 mg N=6	75 mg N=6	100 mg N=6
Mean age (SD), yrs	35.0 (15.10)	27.8 (6.43)	33.7 (17.59)	28.8 (6.37)	37.0 (14.82)	24.3 (2.58)	29.5 (10.65)
Male gender, n (%)	6 (50.0)	4 (66.7)	5 (83.3)	5 (83.3)	3 (50.0)	5 (83.3)	4 (66.7)
Race, n (%)							
White	11 (91.7)	6 (100.0)	6 (100.0)	4 (66.7)	5 (83.3)	5 (83.3)	6 (100.0)
Black	0	0	0	1 (16.7)	0	0	0
Other	1 (8.3)	0	0	1 (16.7)	1 (16.7)	1 (16.7)	0
Mean height, (SD), cm	166.8 (10.31)	175.8 (9.87)	176.0 (9.96)	174.3 (11.15)	173.3 (7.66)	176.5 (9.91)	176.0 (18.22)
Mean weight (SD), kg	73.5 (11.93)	80.5 (23.36)	79.6 (7.21)	79.9 (11.83)	76.9 (10.09)	78.5 (16.08)	79.3 (24.60)
Mean BMI (SD), kg/m^2	26.4 (3.82)	25.6 (5.00)	25.8 (3.38)	26.3 (3.67)	25.6 (2.79)	25.1 (3.40)	24.9 (3.10)

Pharmacokinetics

Figure 2: Mean (+SD) Plasma Concentration Versus Time of IDX184 and the Nucleoside Metabolite (NM)

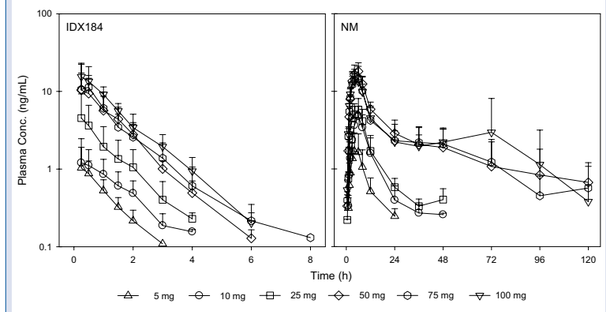
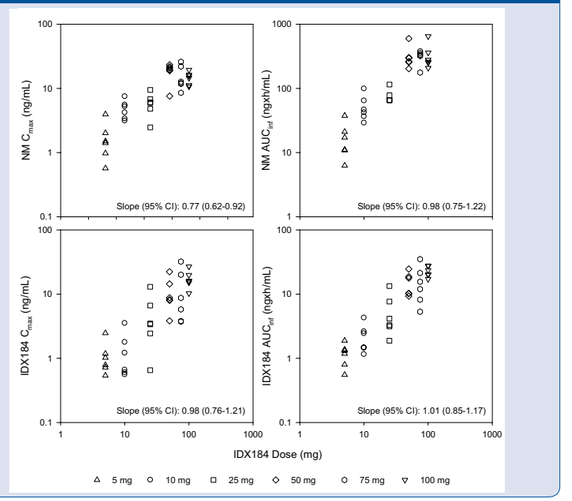


Table 2: Plasma PK Parameters of IDX184 and the Nucleoside Metabolite (NM)

Dose (mg)	Entity	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0\text{-}inf}$ (ng*hr/mL)	$T_{1/2}$* (hr)	C_{24h} (ng/mL)
5	IDX184	1.12±0.70	0.38 (0.23-0.98)	1.19±0.48	0.58±0.14	
	NM	1.74±1.19	4.00 (3.00-6.00)	17.3±11.2	5.42±1.65	0.25±0.06
10	IDX184	1.39±1.15	0.37 (0.25-1.00)	2.22±1.15	1.06±0.37	
	NM	4.82±1.62	6.00 (4.00-6.00)	53.2±25.5	12.2±7.9	0.40±0.21
25	IDX184	4.93±4.40	0.25 (0.25-2.00)	5.53±4.25	0.82±0.23	
	NM	5.93±2.30	6.00 (3.00-8.00)	81.9±23.2	18.0±11.8	0.58±0.17
50	IDX184	10.9±6.52	0.26 (0.23-0.50)	15.2±6.25	0.80±0.16	
	NM	18.6±5.63	6.00 (4.00-6.00)	318±139	22.4±6.7	2.88±1.39
75	IDX184	12.4±11.4	0.49 (0.27-1.50)	16.1±10.6	0.90±0.22	
	NM	15.5±6.81	6.00 (4.00-6.00)	311±78.9	42.5±45.7	2.31±1.46
100	IDX184	17.3±5.55	0.25 (0.25-0.50)	22.7±4.29	0.92±0.19	
	NM	14.6±3.28	5.00 (3.00-6.00)	334±161	19.9±4.72	2.23±0.88

Values are reported as mean ± SD, except for T_{max} where median (min-max) are reported.
*$T_{1/2}$ estimation depended on the actual observed terminal phase and $T_{1/2}$ for the 5 mg and 10 mg doses was underestimated due to a partially observed terminal phase.

Figure 3: Exposure of IDX184 and the Nucleoside Metabolite (NM) Versus Dose



- IDX184 was rapidly absorbed with higher exposure as doses increased from 5 to 100 mg.
- Plasma exposure to IDX184 and the NM was essentially dose proportional and low (with C_{max} < 20 ng/mL), consistent with a liver-targeting approach.
- Unchanged IDX184 exhibited a rapid disposition phase with a consistently short plasma $T_{1/2}$ across all doses; mean elimination $T_{1/2}$ of the NM ranged from 18.0 to 42.5 hr for doses ≥ 25 mg.
- Mean plasma concentration of the NM 24 hr post dosing (C_{24h}) was dose related: 0.25-0.40 ng/mL for the 5 and 10 mg doses, and 0.58-2.88 ng/mL for doses ≥ 25 mg.
- Predicted trough plasma levels of the NM after QD dosing of IDX184 at 25 to 100 mg ranged from 1.2 to 7.4 ng/mL after three doses and from 1.8 to 10.3 at steady-state.

Table 3: Predicted Trough Plasma Levels of the Nucleoside Metabolite (NM)

IDX184 QD Dose (mg)	NM Trough (ng/mL)		
	1st dose[1]	3rd dose[2]	Steady-state[2,3]
25	0.582	1.230	1.776
50	2.880	5.847	8.722
75	2.311	5.640	7.478
100	2.228	7.406	10.266

1: First-in-man single-dose data (mean)
2: Non-compartmental superposition based on single-dose cohort means from first-in-man study.
3: Steady-state is estimated at 5-7 days.

Table 4: Urine PK Parameters of IDX184 and the Nucleoside Metabolite (NM)

Dose (mg)	IDX184			NM		
	$Au_{0\text{-}t}$ (µg)	% Dose Excr	CL_R (mL/min)	$Au_{0\text{-}t}$ (µg)	% Dose Excr*	CL_R (mL/min)
5	10.2±3.7	0.2±0.1	165±30	329.9±144.0	13.9±6.1	289±58
10	17.2±3.8	0.2±0.0	158±55	924.2±530.5	19.5±11.1	272±73
25	51.0±30.8	0.2±0.1	177±46	1423.7±490.2	12.0±4.1	322±61
50	108.5±36.9	0.2±0.1	128±42	4837.3±1705.7	20.4±7.2	271±76
75	122.9±50.7	0.2±0.1	153±54	4565.5±1391.9	12.8±3.9	281±36
100	165.5±36.4	0.2±0.1	123±15	5700.7±2990.8	12.0±6.3	286±51

Values are reported as mean ± SD. * Based on molar ratio

- Cumulative urine excretion of IDX184 increased with dose, but remained consistently low (0.2% of administered doses) across all cohorts.
- Urine NM was quantifiable in all fractions during the 120 hr post dose collection interval. In general, cumulative amount of NM excreted in urine increased with dose.
- Cumulative amount of the NM excreted in urine was higher than IDX184, representing 12 to 20% of administered doses (% molar ratio).
- Near maximum cumulative urine excretion of the NM was reached between 48 and 72 hr.
- Renal clearance remained consistent across cohorts: 123-177 mL/min for IDX184 and 271-322 mL/min for the NM.

Safety

- There were no premature discontinuations, serious adverse events or dose-limiting toxicities.
- There were no patterns in adverse events across the treatment groups **(Table 5)**. All adverse events were mild to moderate in intensity and resolved by the end of the study.
- In addition, there were no discernable patterns in laboratory abnormalities across treatment groups after a single dose.

Table 5: Summary of Treatment-Emergent Adverse Events, n

Parameter	Placebo N=12	5 mg N=6	10 mg N=6	25 mg N=6	50 mg N=6	75 mg N=6	100 mg N=6
Dizziness	3	1	0	1	0	0	0
Dermatitis contact	1	0	0	0	1	0	0
Dysmenorrhoea	1	1	0	0	0	0	0
Fatigue	1	0	0	0	0	1	0
Headache	1	0	0	1	0	0	0
Abdominal distension	1	0	0	0	0	0	0
Arthralgia	0	0	1	0	0	0	0
Back pain	1	0	0	0	0	0	0
Head discomfort	1	0	0	0	0	0	0
Lymphadenopathy	0	0	0	1	0	0	0
Nausea	1	0	0	0	0	0	0
Palpitations	1	0	0	0	0	0	0
Pharyngolaryngeal pain	0	0	0	1	0	0	0
Pruritus	0	0	0	1	0	0	0
Rash	0	0	0	1	0	0	0
Vessel puncture site pain	1	0	0	0	0	0	0

DISCUSSION AND CONCLUSIONS

- IDX184 appeared to be safe and well tolerated in healthy subjects at single doses up to 100 mg.
- Pharmacokinetics of IDX184 and the nucleoside metabolite (NM) are consistent with a liver-targeting approach based on:
  - Low systemic exposures
  - Plasma $T_{1/2}$ of NM approximating the *in vitro* intracellular $T_{1/2}$ of NM-TP in human hepatocytes
- The predicted plasma trough levels of the NM after three daily IDX184 doses of 25, 50, 75 or 100 mg ranged from 1.2 to 7.4 ng/mL. Trough NM concentrations > 2 ng/mL during a 4-day study in HCV-infected chimpanzees led to viral load reduction ≥ 1 log_{10} (see Abstract #583).
- The favorable safety and PK profiles warrant further clinical development of IDX184. A 3-day proof-of-concept study evaluating QD doses of 25, 50, 75 and 100 mg IDX184 in treatment-naïve, genotype-1 HCV-infected patients is ongoing.

References

1. Cretton-Scott E, *et al* (2008). J. Hepatology 48, S220.
2. Standring D, Lanford R, Cretton-Scott E, *et al* (2008). 43rd Conference of the European Association for the Study of the Liver (EASL), Milan, Italy.

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Disclosures

B. Belanger is a former employee of and B. Kuca is a former consultant to Idenix Pharmaceuticals, Inc. All other authors are current employees of Idenix Pharmaceuticals, Inc.

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