

Antiviral Activity, Safety and Pharmacokinetics of IDX184, a Liver-Targeted Nucleotide HCV Polymerase Inhibitor, in Patients with Chronic Hepatitis C

J. Lalezari¹, D. Asmuth², A. Casiro³, H. Vargas⁴, G. Dubuc Patrick⁵, W. Liu⁵, K. Pietropaolo⁵, X.J. Zhou⁵, J. Sullivan-Bólyai⁵, D. Mayers⁵ and the IDX-08C-003 Investigator Group

¹Quest Clinical Research, San Francisco, CA; ²Clinical and Translational Science Center-University of California Davis, Sacramento, CA; ³Acilres, Hospital Privado Modelo, Buenos Aires, Argentina; ⁴Mayo Clinic Arizona, Phoenix, AZ; ⁵Idenix Pharmaceuticals, Inc., Cambridge, MA

BACKGROUND

IDX184 is a liver-targeted, oral nucleotide prodrug of 2'-methylguanosine monophosphate (2'-MeGMP). The prodrug is designed to enhance formation of its active triphosphosphate (2'-MeGTP) within hepatocytes, while minimizing systemic exposure to the parent drug and its nucleoside metabolite (2'-MeG). IDX184 is a potent and selective inhibitor of the HCV NS5B polymerase *in vitro* and demonstrated multilog viral load reductions in HCV-infected chimpanzees receiving 10 mg/kg for 4 days.^{1,2} In healthy volunteers, single oral doses up to 100 mg were safe and well-tolerated. Systemic exposure of IDX184 and 2'-MeG was low, with pharmacokinetics (PK) supporting once-daily dosing.³

OBJECTIVES

- To investigate safety and tolerability of IDX184 administered for 3 days to HCV-infected patients
- To determine antiviral activity of IDX184
- To evaluate plasma PK of IDX184 and 2'-MeG
- To guide dose selection for Phase II studies

METHODS

Patients and Study Design

- Randomized, double-blind, placebo-controlled, sequential cohort, dose-escalation study
- Treatment-naïve, male and female patients between 18 and 65 years of age with genotype 1, chronic HCV infection (at least 6 months)
- Enrolled patients had BMI ≤ 32 kg/m², HCV RNA ≥ 5 log₁₀ IU/mL, ALT ≤ 2.5xULN and compensated liver disease.
- Sequential cohorts of 10 patients, randomized 8:2 (active:placebo), received 25, 50, 75 or 100 mg of IDX184 orally once-daily for three days and were monitored for 14 additional days.
- Safety data were reviewed at the end of each dosing cohort, prior to escalating to the next sequential dose.

Analysis

- HCV RNA was quantitated by a validated real-time RT-PCR assay using the COBAS[®] TaqMan[®] platform, with a measurement range of 50-50,000,000 IU/mL.
- PK sampling was performed over 8 hours on Days 1 and 3. Plasma concentrations of IDX184 and 2'-MeG were determined using validated LC-MS/MS methodologies. The lower limit of quantitation was 0.1 and 0.2 ng/mL for IDX184 and 2'-MeG, respectively.
- Safety measurements included clinical history, routine laboratory evaluations, physical examination, 12-lead ECGs, vital signs, and adverse event assessments.

RESULTS

Demographic and Baseline Characteristics

41 patients were enrolled. The treatment groups were comparable at baseline (Table 1).

Table 1: Demographic and Baseline Characteristics

Parameter	Placebo n=8	25 mg n=8	50 mg n=8	75 mg n=8	100 mg n=9*
Mean age (SD), yrs	49.3 (7.63)	48.3 (6.50)	48.8 (5.85)	47.3 (8.12)	47.2 (7.89)
Gender, n					
Female	3	2	1	2	4
Male	5	6	7	6	5
Race, n					
Black	2	2	2	0	1
White	6	5	5	8	7
Other	0	1	1	0	1
Mean BMI (SD), kg/m ²	25.9 (3.70)	28.4 (4.01)	27.6 (3.40)	27.0 (3.18)	26.5 (4.59)
Mean HCV RNA (SD), log ₁₀ IU/mL	6.40 (0.858)	6.34 (0.479)	6.74 (0.472)	6.47 (0.286)	6.40 (0.551)
HCV genotype 1a/1b, n	5/3	6/2	7/1	7/1	7/2
Mean ALT (SD), U/L	45.4 (28.19)	44.8 (31.06)	56.0 (27.90)	55.1 (24.11)	52.2 (26.19)

*Cohort overenrolled 1 patient.

Efficacy

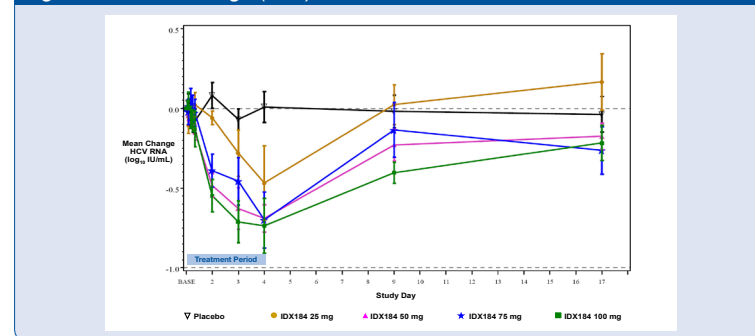
- Mean HCV RNA reductions ranged from 0.47 log₁₀ in the 25 mg IDX184 cohort to 0.74 log₁₀ in the 100 mg IDX184 cohort after three days of dosing (Table 2 and Figure 1).
- The number of patients with ≥1 log₁₀ reduction in HCV RNA at Day 4 increased with IDX184 dose (Table 2).

Table 2: HCV RNA Change at Day 4 (End of Treatment)

Cohort	Dose (mg/day)	Mean Change +/- SE in HCV RNA (log ₁₀) at Day 4	Patients with ≥1 log ₁₀ Reduction in HCV RNA at Day 4
A (n=6*)	25	-0.47 ± 0.23	1
B (n=8)	50	-0.69 ± 0.09	1
C (n=8)	75	-0.70 ± 0.18	2
D (n=9)	100	-0.74 ± 0.17	4
Control (n=8)	Placebo	+0.01 ± 0.10	0

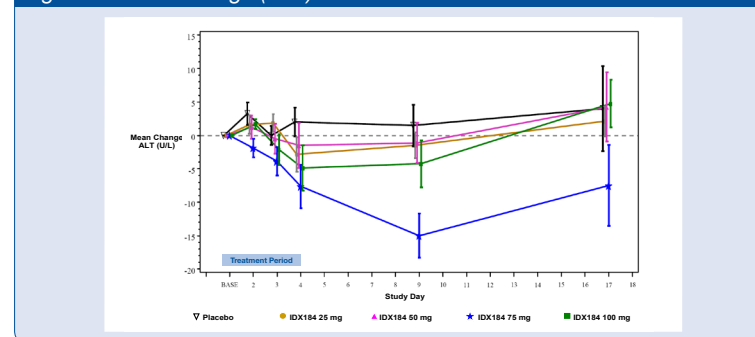
*Eight patients were randomized. Two patients excluded from analysis due to dosing errors (>1 dose of 50 mg). Excluded patients had viral load declines of approximately 0.5 log₁₀ at end of treatment.

Figure 1: Mean Change (±SE) in HCV RNA



- During the treatment period, mean ALT (and AST) levels tended to decrease from baseline in the IDX184 cohorts. This was most clearly seen in the 75 mg and 100 mg IDX184 cohorts (Figure 2).

Figure 2: Mean Change (±SE) in ALT



Pharmacokinetics

- IDX184 was rapidly absorbed with transient plasma exposure after oral dosing (Figure 3).
- Plasma exposure of IDX184 and 2'-MeG was dose-related and low, consistent with a liver-targeting approach (Tables 3 and 4).
- There was no accumulation for IDX184 after multiple dosing (Figure 3 and Table 3); 2'-MeG plasma levels were higher on Day 3 than on Day 1, consistent with the long intracellular T_{1/2} of 2'-MeGTP and QD dosing (Figure 4 and Table 4).

Figure 3: Mean (±SD) IDX184 Plasma Concentrations

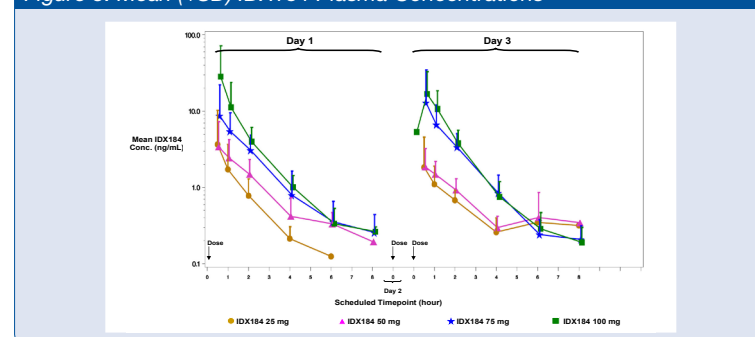


Table 3: Plasma PK Parameters of IDX184

Dose (mg)	PK Day	C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-24h} (ng*hr/mL)	T _{1/2} (hr)
25	1	3.51±5.82	0.60 (0.50-1.02)	4.34±4.84	1.32±0.55
	3	2.19±2.41	1.00 (0.52-2.00)	9.64±6.19	11.8±15.6
50	1	3.85±3.66	0.75 (0.50-2.02)	7.26±4.43	1.19±0.28
	3	2.03±1.16	1.00 (0.50-2.02)	4.53±2.17	1.52±1.22
75	1	9.56±13.1	0.98 (0.50-2.13)	14.9±12.0	1.13±0.20
	3	12.9±19.8	0.99 (0.45-2.00)	17.8±16.2	1.13±0.24
100	1	26.3±41.1	0.58 (0.50-2.02)	30.4±30.9	1.23±0.40
	3	14.7±11.8	0.83 (0.50-2.00)	19.2±12.5	1.07±0.43

Values are reported as means ± SD, except for T_{max} where medians (min-max) are reported.

Figure 4: Mean (±SD) 2'-MeG Plasma Concentrations

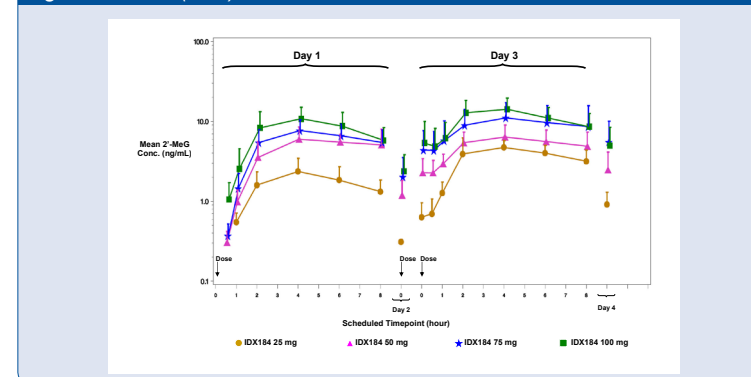


Table 4: Plasma PK Parameters of 2'-MeG

Dose (mg)	PK Day	C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-24h} (ng*hr/mL)	T _{1/2} (hr)	C _{24h} (ng/mL)
25	1	2.40±1.05	4.00 (2.17-8.00)	25.2±9.86	6.27±1.22	0.31±0.03
	3	4.96±0.92	2.00 (2.00-6.00)	56.3±14.3	7.96±1.19	0.91±0.39
50	1	7.30±2.71	5.01 (4.00-8.00)	84.0±28.8	8.04±2.79	1.20±0.62
	3	6.64±2.59	4.00 (2.00-8.00)	97.5±43.1	13.3±6.20	2.48±1.65
75	1	7.78±2.73	4.00 (2.00-6.72)	116.6±60.3	8.34±1.80	2.03±1.50
	3	11.7±6.70	4.00 (3.00-8.00)	183.9±144.0	23.1±7.63	5.53±4.57
100	1	11.4±4.85	4.07 (2.00-6.00)	145.2±59.3	9.02±3.83	2.36±1.47
	3	14.1±5.26	4.00 (0.00-4.00)	178.9±82.6	17.2±10.3	4.99±3.41

Values are reported as means ± SD, except for T_{max} where medians (min-max) are reported. *AUC_{0-24h} for Day 1 and AUC_{0-24h} for Day 3 are reported.

PK/PD Relationships

- Greater HCV RNA and ALT reductions were associated with higher plasma exposure of 2'-MeG (Figures 5 and 6).

Figure 5: Relationship Between HCV RNA Change on Day 4 and Total Exposure of 2'-MeG on Day 1

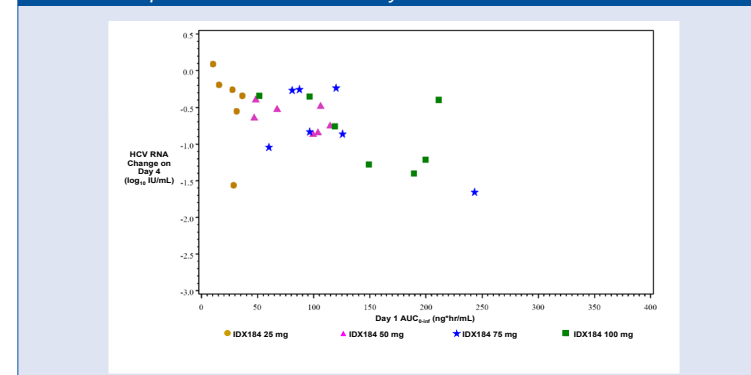
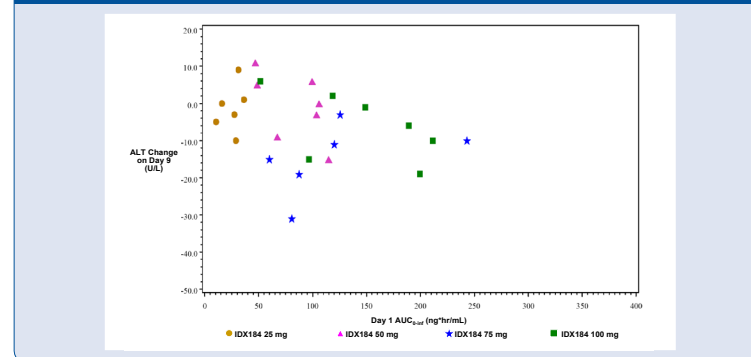


Figure 6: Relationship Between ALT Change on Day 9 and Total Exposure of 2'-MeG on Day 1



Safety

- There were no safety-related treatment discontinuations or serious adverse events.
- Adverse events and laboratory abnormalities observed were similar between IDX184- and placebo-treated patients (Table 5).
- There were no Grade 4 laboratory abnormalities. Grade 3 laboratory abnormalities were single elevations which decreased, on-treatment, to within normal limits or grade 1 levels at the next visit.

Table 5: Treatment-Emergent Adverse Events (>1 patient) and Grade 3 Laboratory Abnormalities, n

Adverse Event	Placebo n=8	25 mg n=8	50 mg n=8	75 mg n=8	100 mg n=9
Headache	1	0	1	2	1
Diarrhea	1	0	1	0	0
Dizziness	1	0	0	1	0
Laboratory Parameter					
Amylase (2.1-5.0 xULN)	1	0	0	0	1*
Lipase (3.1-5.0 xULN)	0	1	0	0	1*
INR/PT (1.5-3.0 xULN)	0	0	0	0	1
Urine erythrocytes	0	0	0	0	1*

*49 year old female with menstrual bleeding

DISCUSSION AND CONCLUSIONS

- IDX184, a liver-targeted prodrug of 2'-MeGMP, delivered significant antiviral activity with low systemic exposures to IDX184 and 2'-MeG.
- IDX184, with much smaller doses administered once daily, demonstrated comparable anti-HCV activity in patients after 3 days versus HCV nucleoside analogs.
- PK/PD relationships between HCV RNA/ALT reductions and 2'-MeG exposure suggest higher IDX184 doses may result in greater viral load reduction with improvement in liver injury parameters.
- IDX184 was safe and well-tolerated in this study.
- Further evaluation of IDX184 in combination with pegylated interferon and ribavirin in HCV-infected patients is planned.

References

- Cretton-Scott E, et al (2008). Journal of Hepatology; Vol 48, Page S220.
- Standing D, et al (2008). Journal of Hepatology; Vol 48, Page S30.
- Zhou XJ, et al (2009). Journal of Hepatology; Vol 50, Page S351.

Acknowledgments

A portion of this research at the Clinical and Translational Science Center-University of California Davis, Sacramento, CA was made possible by Grant Number UL1 RR024146 from the National Center for Research Resources (NCR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. We thank Teresa Dahlman for assistance with the poster preparation.