

Antiviral Activity, Pharmacokinetics and Safety of IDX184 in Combination with Pegylated Interferon (pegIFN) and Ribavirin (RBV) in Treatment-Naïve HCV Genotype 1-Infected Subjects

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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 triphosphate (2'-MeGTP) within hepatocytes, while minimizing systemic exposure to the parent drug and its nucleoside metabolite (2'-MeG). The active triphosphate, 2'-MeGTP, is a potent and selective inhibitor of the hepatitis C virus (HCV) NS5B polymerase. After single and multiple doses for three days, IDX184 was generally safe and well tolerated up to 100 mg/day in both healthy volunteers and HCV-infected subjects, respectively^{1,2}. Mean viral load reductions after three days of IDX184 monotherapy in treatment-naïve HCV genotype 1-infected subjects ranged from 0.47 log₁₀ IU/mL at 25 mg/day to 0.74 log₁₀ IU/mL at 100 mg/day².

This presentation summarizes key preliminary results from the 50 and 100 mg cohorts of the ongoing Phase IIa study of IDX184 in combination with pegIFN and RBV for 14 days.

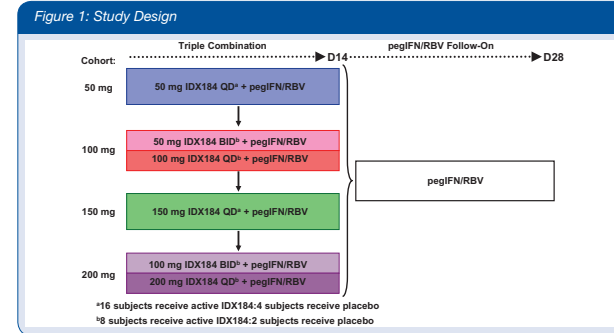
OBJECTIVES

- To evaluate safety and tolerability of IDX184 in combination with pegIFN and RBV (P/R) administered for 14 days to HCV-infected subjects
- To evaluate antiviral activity of IDX184 in combination with pegIFN and RBV
- To evaluate plasma pharmacokinetics (PK) of IDX184 and 2'-MeG
- To guide dose selection for Phase IIb studies

METHODS

Study Design and Subjects

- Randomized, double-blind, placebo-controlled, sequential cohort, dose-escalation study
- Treatment-naïve, male and female subjects between 18 and 65 years of age with genotype 1, chronic HCV infection
- Enrolled subjects have BMI ≤ 35 kg/m², HCV RNA ≥ 5 log₁₀ IU/mL, ALT ≤ 3 x upper limit of normal (ULN) and compensated liver disease.
- Sequential cohorts of 20 subjects, randomized 16:4 (active:placebo), are administered 50, 100, 150 or 200 mg/day of IDX184 orally for 14 days in combination with pegIFN/RBV, which then continues for an additional 14 days. Upon completion of the study, subjects are offered extended pegIFN/RBV treatment for up to 48 weeks.
 - IDX184 dosing for all subjects in the 50 and 150 mg cohorts is once daily. In the 100 and 200 mg cohorts, half of the subjects are dosed once daily (100 or 200 mg QD) and the other half are dosed twice daily (50 or 100 mg BID) with IDX184.
 - PegIFN alpha-2a is administered subcutaneously at a dose of 180 µg once per week.
 - RBV is administered orally at a dose of 1000-1200 mg (weight-based) daily.
 - A schematic of the study design is displayed in Figure 1.
- Safety data for each dosing cohort are reviewed by an external Steering Committee prior to escalating to the next sequential dose.



Analysis

- The primary antiviral activity endpoint is the change in HCV RNA level from baseline to Day 14. HCV RNA is quantitated by a validated real-time PCR assay (COBAS® TaqMan®), with a lower limit of detection of 15 IU/mL. Data presented are as-observed, with no imputation of missing values.
- Intensive PK sampling is performed over 8 hours on Days 0 and 10, with trough samples obtained on Days 3, 7 and 14. Plasma concentrations of parent IDX184 and 2'-MeG are determined using validated LC-MS/MS methodologies. The lower limit of quantitation is 0.1 and 0.2 ng/mL for IDX184 and 2'-MeG, respectively.
- The relationship between plasma 2'-MeG C_{trough} concentration and HCV RNA reduction at Day 14 is examined using an E_{max} modeling approach. For this analysis, the mean of 2'-MeG C_{trough} concentrations for each subject at Days 3, 7, 10 and 14 is used.
- A stepwise regression analysis of the viral load response at Day 14 is performed. Parameters include age, race, sex, height, weight, BMI, baseline viral load, baseline ALT, HCV sub-type and mean plasma 2'-MeG C_{trough} concentrations.
- Safety measurements include clinical history, routine laboratory evaluations, physical examination, 12-lead ECGs, vital signs and adverse event assessments.
- Data are summarized descriptively, with placebo subjects pooled across cohorts. Subjects in the QD and BID subgroups within the 100 mg cohort are also pooled for safety analyses, since statistical analysis of demographic and baseline characteristics as well as review of adverse events and safety laboratory parameters, demonstrated the similarity of the two groups.
- This study is ongoing. These data summarize key preliminary results from the 50 and 100 mg cohorts, with final analyses pending.

RESULTS

Demographic and Baseline Characteristics

- A total of 40 subjects were enrolled in the 50 mg and 100 mg cohorts. The cohorts were generally comparable at baseline (Table 1).

Table 1: Demographic and Baseline Characteristics

Parameter	Placebo P/R N=8	50 mg QD+P/R N=16	50 mg BID+P/R N=8	100 mg QD+P/R N=8
Mean age (SD), yrs	48 (5.1)	51 (9.8)	50 (11)	48 (12)
Gender, n (%)				
Female	4 (50%)	2 (13%)	3 (38%)	3 (38%)
Male	4 (50%)	14 (88%)	5 (63%)	5 (63%)
Race, n (%)				
Black	3 (38%)	5 (31%)	3 (38%)	2 (25%)
White	4 (50%)	9 (56%)	5 (63%)	5 (63%)
Other	1 (13%)	2 (13%)	0	1 (13%)
Mean BMI (SD), kg/m ²	29 (3.3)	27 (4.1)	29 (3.6)	29 (4.1)
Mean HCV RNA (SD), log ₁₀ IU/mL	6.4 (0.53)	6.1 (0.64)	6.3 (0.47)	6.4 (0.55)
HCV genotype 1a/1b, n	6/2	12/4	6/1*	7/1
Mean ALT (SD), U/L	59.6 (25.3)	63.4 (33.1)	57.7 (38.0)	65.0 (24.8)

*The genotype 1b sub-type could not be identified in one subject.

Safety Summary

- Adverse events, laboratory abnormalities, vital signs and ECGs were consistent between placebo and IDX184-treated cohorts in combination with pegIFN/RBV administration (Table 2).

Table 2: Treatment-Emergent Adverse Events (>2 subjects) and Grade 3/4 Laboratory Abnormalities

Adverse Event	Placebo+P/R N=8	IDX184 50 mg QD+P/R N=16	IDX184 100 mg +P/R* N=16
Fatigue	3 (38%)	9 (56%)	2 (13%)
Myalgia	2 (25%)	7 (44%)	4 (25%)
Headache	4 (50%)	2 (13%)	4 (25%)
Nausea	1 (13%)	4 (25%)	4 (25%)
Chills	2 (25%)	4 (25%)	1 (6%)
Diarrhea	1 (13%)	0	3 (19%)
Irritability	0	1 (6%)	3 (19%)
Insomnia	1 (13%)	1 (6%)	1 (6%)
Pyrexia	0	1 (6%)	2 (13%)
Laboratory Parameter			
Neutrophil decrease (≤749/mm ³)	2 (25%)	3 (19%)	1 (6%)
Triglyceride increase (≥751 mg/dL)	0	0	1 (6%)

*QD and BID dosing regimens are combined.

- Most clinical adverse events were mild. There were no serious adverse events in subjects receiving IDX184 with pegIFN/RBV through Day 14.
- Two subjects had grade 1 creatinine elevations that resulted in interruption of study drugs. The elevations occurred on Day 7 in a subject receiving 50 mg IDX184 BID and on Day 10 in a subject receiving 100 mg IDX184 QD. The creatinine levels subsequently normalized and study drugs were re-started. Both subjects were started on ibuprofen at the beginning of the study. There were no discernable patterns for renal parameters among the IDX184 and placebo-treated cohorts.

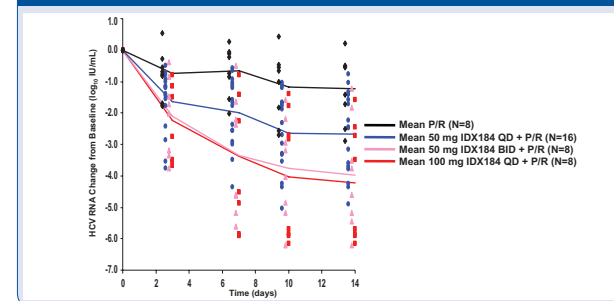
Antiviral Activity

Table 3: Antiviral Activity of IDX184 in Combination with pegIFN/RBV

Cohort	Mean Change +/- SD in HCV RNA (log ₁₀ IU/mL) at Day 14	Subjects with Undetectable Viral Load at Day 14 (<15 IU/mL)
Placebo + P/R (N=8)	-1.2 ± 1.1	0 (0%)
50 mg IDX184 QD + P/R (N=16)	-2.7 ± 1.3	2 (13%)
50 mg IDX184 BID + P/R (N=8)	-4.0 ± 1.7	4 (50%)
100 mg IDX184 QD + P/R (N=8)	-4.2 ± 1.9	4 (50%)

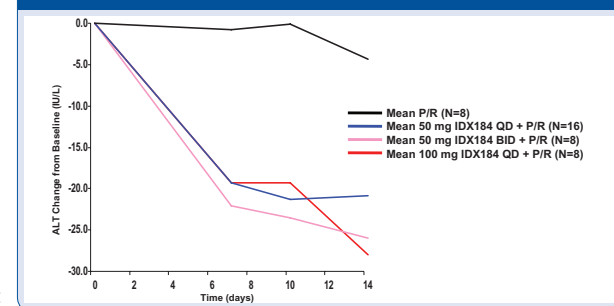
*Placebo group will change as additional cohorts are added to the study.

Figure 2: Mean and Individual HCV RNA Changes in the 50 and 100 mg IDX184 Cohorts



- Viral load response was IDX184 dose dependent, with mean HCV RNA reductions of 1.2, 2.7, 4.0 and 4.2 log₁₀ IU/mL in the placebo, 50 mg IDX184 QD, 50 mg IDX184 BID and 100 mg IDX184 QD cohorts, respectively (Table 3 and Figure 2).
- Antiviral activity in the 50 mg IDX184 BID and 100 mg IDX184 QD cohorts was similar.
- The number of subjects with undetectable HCV RNA at Day 14 was also IDX184 dose dependent. In both 100 mg cohorts (50 mg BID and 100 mg QD), 50% of the subjects achieved undetectable HCV RNA at Day 14 (Table 3).
- None of the subjects experienced virologic breakthrough (defined as a 1 log₁₀ IU/mL increase of HCV RNA above nadir) during treatment with IDX184 in combination with pegIFN and RBV.
- In contrast to pegIFN/RBV alone (placebo), mean ALT (and AST) levels markedly decreased from baseline (normalized) in all IDX184-treated cohorts (Figure 3).

Figure 3: Mean ALT Changes in the 50 and 100 mg IDX184 Cohorts



Plasma Pharmacokinetics

- Parent IDX184 was rapidly cleared from plasma and no accumulation was observed over time (Day 0 and Day 10, Figure 4). In the 50 mg QD and 50 mg BID cohorts, IDX184 had similar C_{max} and AUC values, approximately half of those measured with 100 mg QD (Table 4).
- Plasma exposure (C_{max} and AUC) of 2'-MeG approximately doubled on Day 10 as compared to the first dose (Figure 4 and Table 5).

- The 50 mg BID cohort achieved higher 2'-MeG C_{trough} concentrations than the 50 mg QD cohort while maintaining a lower C_{max} compared to the 100 mg QD cohort (Figure 4 and Table 5).
- The 50 mg BID and 100 mg QD cohorts had comparable 2'-MeG C_{trough} concentrations (Table 5). After multiple dosing, 2'-MeG C_{trough} concentrations were consistent between Day 3 and Day 14 (Figure 5).

Figure 4: Mean (+SD) Plasma Concentrations of IDX184 and 2'-MeG Over Time

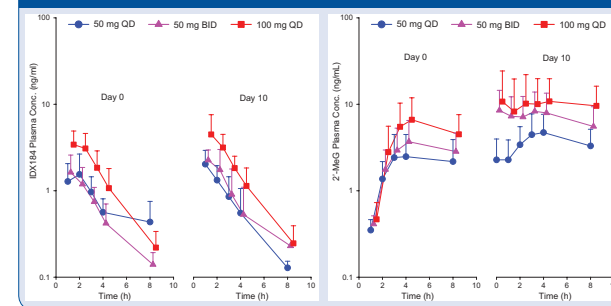


Figure 5: Mean (+SD) Plasma C_{trough} Concentrations of 2'-MeG Over Time

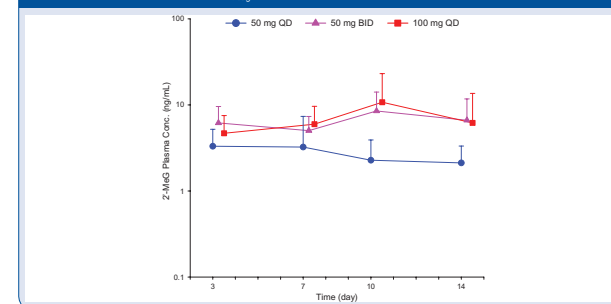


Table 4: Plasma Pharmacokinetic Parameters of IDX184

IDX184 Dose	Day	C _{max} (ng/mL)	T _{max} (h)	AUC ₀₋₈ (ng·h/mL)	T _{1/2} (h)
50 mg QD	0	1.86±0.98	2.0 (1.0-8.0)	4.48±1.65	1.61±0.96
	10	2.16±0.83	1.0 (1.0-4.0)	4.70±1.97	1.41±0.72
50 mg BID	0	1.71±0.86	1.5 (1.0-3.0)	3.87±1.45	1.27±0.75
	10	2.49±0.92	1.0 (1.0-2.0)	5.35±3.52	1.13±0.33
100 mg QD	0	3.72±1.55	1.0 (1.0-3.0)	10.5±4.99	1.59±0.68
	10	4.74±2.93	1.5 (1.0-4.0)	11.4±4.95	1.35±0.42

Values are reported as mean ± SD, except for T_{max}, where median (min-max) is reported.

Table 5: Plasma Pharmacokinetic Parameters of 2'-MeG

IDX184 Dose	Day	C _{trough} (ng/mL)	T _{max} (h)	AUC ₀₋₈ (ng·h/mL)	T _{1/2} (h)	C _{trough} ^b (ng/mL)
50 mg QD	0	2.85±2.04	4.0 (3.0-8.0)	13.8±9.8	4.0±1.1	2.69±1.84 (0.48-7.58)
	10	4.94±3.20	4.0 (0.0-8.0)	29.2±17.1	8.3±4.8	
50 mg BID	0	3.81±2.71	4.0 (3.0-8.0)	18.2±13.7	4.1	7.24±4.44 (2.68-16.1)
	10	9.40±6.69	3.0 (0.0-4.0)	50.7±38.2	8.0±3.2	
100 mg QD	0	7.11±4.97	4.0 (3.0-8.0)	34.0±25.3	11.7	6.31±5.95 (0.89-19.3)
	10	12.6±10.6	4.0 (0.0-8.0)	77.6±73.0	8.9±1.7	

Values are reported as mean ± SD, except for T_{max}, where median (min-max) is reported. The range is also reported for C_{trough} concentrations.

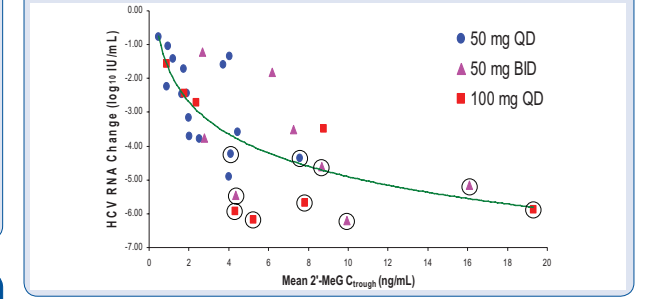
^aHalf-life estimated using samples collected up to 8 hours.

^bMean of 2'-MeG C_{trough} concentrations at Days 3, 7, 10 and 14.

PK/PD Relationships

- E_{max} modeling confirmed a clear PK/PD relationship between the HCV viral load decline at Day 14 and mean 2'-MeG C_{trough} concentrations measured during treatment (p<0.0001, Figure 6).
- In a stepwise regression analysis which included all baseline characteristics, mean plasma 2'-MeG C_{trough} concentrations during treatment was the only significant predictor (p=0.0001) of the HCV viral load decline at Day 14.

Figure 6: E_{max} Model - Relationship Between HCV RNA Decline at Day 14 and Mean Plasma 2'-MeG C_{trough} Concentrations*



*Mean of the Day 3, 7, 10 and 14 2'-MeG C_{trough} concentrations for each subject; circled data points indicate subjects who had undetectable HCV RNA (<15 IU/mL) at Day 14.

DISCUSSION AND CONCLUSIONS

- IDX184, a liver-targeted prodrug of 2'-MeGMP, delivers significant antiviral activity with low systemic exposures to IDX184 and 2'-MeG.
- In this ongoing study, IDX184 demonstrated potent, dose-dependent antiviral activity when combined with pegIFN and RBV. At Day 14, mean HCV RNA reductions were 1.2, 2.7, 4.0 and 4.2 log₁₀ IU/mL in the placebo, 50 mg IDX184 QD, 50 mg IDX184 BID and 100 mg IDX184 QD cohorts, respectively. Half of the subjects receiving a total daily dose of 100 mg IDX184 in combination with pegIFN/RBV achieved undetectable HCV RNA levels by Day 14. Liver injury parameters (ALT and AST) improved (normalized) with all doses of IDX184.
- Antiviral activity and safety parameters measured after a total daily dose of 100 mg were not affected by a QD or BID dosing regimen.
- After multiple dosing, no accumulation of IDX184 was observed and levels of 2'-MeG remained constant.
- There was a strong PK/PD relationship between mean plasma 2'-MeG C_{trough} concentrations and HCV RNA reduction at Day 14. In the stepwise regression analysis presented, plasma 2'-MeG C_{trough} concentration was the only significant predictor of viral load decline at Day 14 (p=0.0001).
- At daily doses of 50 mg and 100 mg of IDX184 in combination with pegIFN/RBV, the side effect profile of the three drug combination was consistent with the known side effect profile of pegIFN/RBV alone.
- An external Steering Committee reviewed all safety data of the 50 and 100 mg cohorts and recommended initiation of the 150 mg cohort.

REFERENCES

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DISCLOSURES

G. Dubuc Patrick, J. Chen, K. Pietropaolo, X.J. Zhou, J. Z. Sullivan-Bólyai and D. Mayers are employees of Idenix Pharmaceuticals, Inc.