This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

2 Synopsis

Name of finished product: IDX184

[redacted]

Study Description

Title of study: A Phase I/II, Double-Blind, Dose-Escalation Study to Evaluate the Safety and Antiviral Activity of IDX184 in Treatment-Naïve Subjects Infected with Genotype 1 Chronic Hepatitis C

Investigator: [redacted] (Principal Investigator)

Study center: [redacted] United States

Publication (reference): None

Study Methods

Study period:

First subject enrolled: 25-November-2008 (first subject consented)

Last subject completed: 10-July-2009 (last Day 17 visit)

Objectives, development phase, study status:

This is a completed phase I/II study.

The primary objective was:

- To investigate safety and tolerability of IDX184

The secondary objective was:

- To determine antiviral activity of IDX184

[redacted]

Methodology and treatment duration: This was a randomized, double-blind, placebo-controlled, stepwise, sequential cohort study. Treatment-naïve subjects with genotype 1, chronic hepatitis C infection were randomized to receive IDX184 monotherapy or placebo over three days. Oral, once daily (QD) IDX184 doses evaluated were 25 mg, 50 mg, 75 mg and 100 mg. A Steering Committee reviewed the safety data at the completion of each dosing cohort, prior to escalating to the next dose level.

[redacted] Antiviral activity and safety evaluations were performed throughout the study. All subjects were followed through Day 17. After Day 17, standard of care therapy (peginterferon/RBV) may have been initiated at the discretion of the investigator/subject. Any subjects who did not initiate another HCV treatment were to return for four additional follow-up visits (30, 60, 90 and 180 days following the last dose of study medication).

Number of subjects (planned and analyzed): Forty (40) subjects, ten (10) per cohort, were planned to be randomized in an 8:2 ratio to receive either active drug or placebo.

45 subjects were randomized, although, four were not treated. Therefore, 41 subjects comprised the ITT and safety populations. Three subjects described in [Section 10.2, IDX-08C-003 Clinical Study

Report] were excluded from the efficacy evaluable population (38 subjects), and two of the three were excluded from the pharmacokinetics population (39 subjects).

Diagnosis and main criteria for inclusion: Treatment-naïve subjects with genotype 1 chronic hepatitis C infection, plasma HCV RNA ≥ 5 $\log_{10}$ IU/mL and compensated liver disease were enrolled.

Full inclusion/exclusion criteria are listed in [Section 5 of Protocol IDX-08C-003].

Test product and reference therapy – dose, dosage form, administration mode, and batch numbers:

The investigational products were:

- Test product:

Code name: IDX184

Manufacturer: Patheon Pharmaceuticals for Idenix Pharmaceuticals, Inc.

Dosage form: 25-mg capsules

Vendor Batch #/Lot No.: [redacted]

- Reference product:

Code name: Placebo for IDX184

Manufacturer: Patheon Pharmaceuticals Inc. for Idenix Pharmaceuticals, Inc.

Dosage form: 25-mg matching placebo capsules

Vendor Batch #/ Lot No.: [redacted]

Criteria for evaluation

Efficacy:

A central laboratory utilized a validated, laboratory developed assay for the quantification of HCV viral RNA load which utilized extracted plasma for analysis on the COBAS® Taqman instrument for PCR amplification. This real time PCR assay quantitates HCV viral RNA with a measurement range of 50-50,000,000 IU/ml.

[redacted]

Safety:

Safety and tolerability measurements included clinical laboratory evaluations, physical examination, vital signs, 12-lead ECGs, AE assessments and dose-limiting toxicity assessments as defined in [Section 7.5.1.1 of Protocol IDX-08C-003].

Triplicate ECGs were acquired in a standardized fashion and read centrally, by a blinded cardiologist. Quantitative parameters (including QTc), descriptive assessments of rhythm and morphology, and a global assessment of normality were reported.

Statistical methods:

Data were summarized using descriptive statistics. Details of the analysis are provided in [Section 9.7, IDX-08C-003 Clinical Study Report] and the Statistical Analysis Plan [Appendix 16.1.9].

Summary - Conclusions

Efficacy

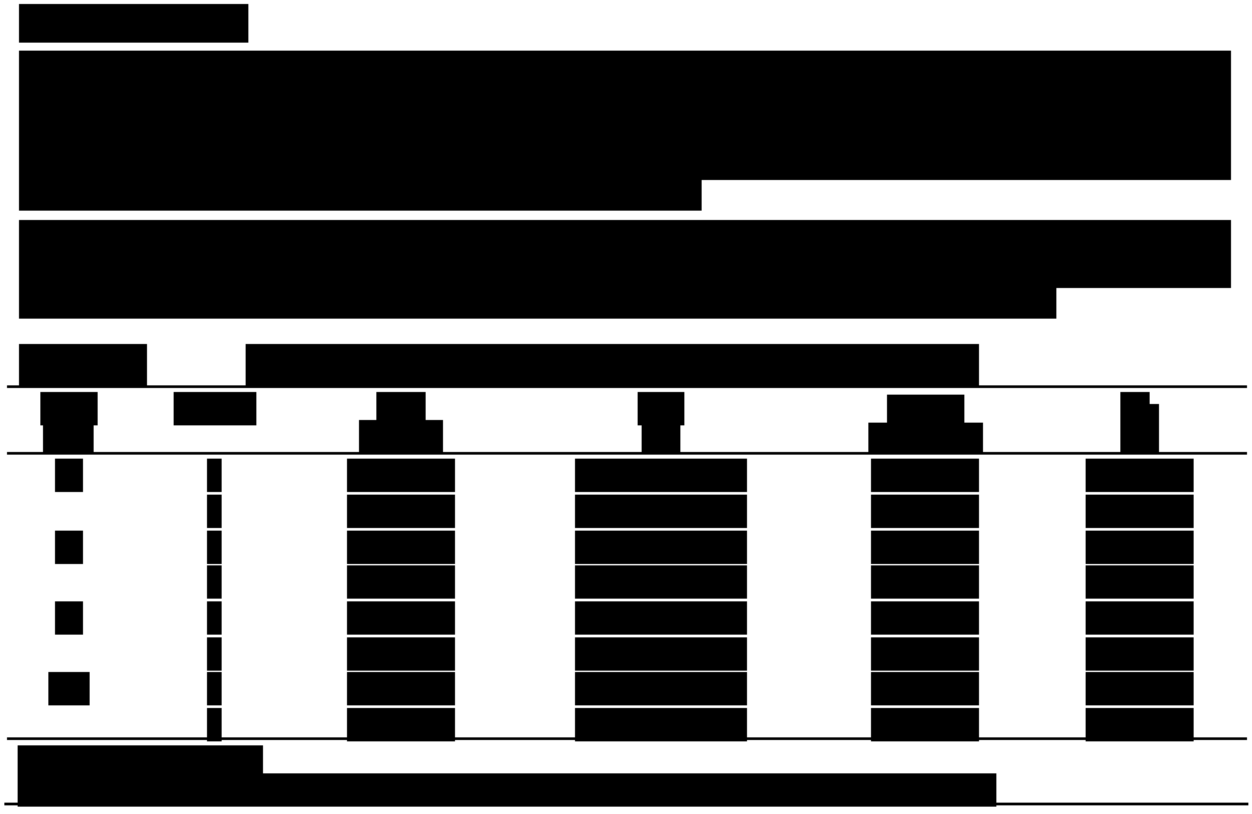
For the efficacy evaluable population, changes from baseline in plasma HCV RNA after three days of dosing (Day 4) are presented in Table 2-1.

Table 2-1 Change from baseline in HCV RNA at Day 4 (log_{10} IU/mL, efficacy evaluable population)

Visit	Statistic	Placebo N=8	IDX184 25 mg N=6	IDX184 50 mg N=8	IDX184 75 mg N=7	IDX184 100 mg N=9
Day 4	n	8	6	8	7	9
	Mean (SE)	-0.05 (0.091)	-0.47 (0.234)	-0.69 (0.086)	-0.56 (0.129)	-0.69 (0.170)
	Median	-0.11	-0.30	-0.69	-0.48	-0.61
	SD	0.256	0.574	0.243	0.340	0.510
	25%, 75%	-0.22, 0.01	-0.55, -0.19	-0.84, -0.49	-0.86, -0.25	-1.21, -0.35
	Min, Max	-0.3, 0.5	-1.6, 0.1	-1.1, -0.4	-1.0, -0.2	-1.4, 0.1

Source: Table 14.2-1.3
Data presented as-observed.

During the treatment period, mean ALT and AST levels tended to decrease from baseline in the IDX184 groups. This was most clearly seen in the 75 mg and 100 mg IDX184 groups.



Safety

There were no safety-related premature treatment discontinuations and no serious adverse events (SAEs) were reported.

AEs and laboratory abnormalities observed in the study were unrelated to dose and without a discernable pattern. Most AEs were mild or moderate in intensity, transient and had resolved by Day 17.

No clinically meaningful changes were seen in vital sign measurements or physical examination findings. There were no clinically significant ECG abnormalities.

Conclusions

- At Day 4, mean HCV RNA viral load reductions ranged from 0.47 log_{10} to 0.69 log_{10} at the IDX184 doses evaluated. This compared to a mean HCV RNA reduction of 0.05 log_{10} in the placebo group.
- During the treatment period, mean ALT and AST levels tended to decrease from baseline in the IDX184 groups. This was most clearly seen in the 75 mg and 100 mg IDX184 groups.
-
- At oral doses of 25 mg, 50 mg, 75 mg and 100 mg QD for 3 days, IDX184 appeared to be safe and well tolerated in treatment-naïve, genotype 1 HCV-infected subjects.
- There were no safety-related treatment discontinuations or SAEs.
- There were no discernable patterns in adverse events or laboratory abnormalities between IDX184 treatment groups and placebo. There were no clinically significant ECG abnormalities.
- The favorable safety, antiviral activity and of IDX184 warrant further evaluation in later phase clinical studies in combination with pegylated interferon and ribavirin.

Date of the report: 28-Jan-2010