

A Phase IIa Study of IDX184 in Combination with Pegylated Interferon (pegIFN) and Ribavirin (RBV) in Treatment-Naïve Genotype 1 HCV-Infected Subjects

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I have been a consultant and/or clinical investigator on studies of Hepatitis C for the following sponsors:

- Idenix
- Pharmasset
- Vertex
- Boehringer-Ingelheim
- Bristol-Myers Squibb
- Roche
- Pfizer
- Medarex
- Scynexis
- Achillion

AND

My presentation does include discussion of investigational use of IDX184.

IDX184: Liver-Targeted Nucleotide HCV Polymerase Inhibitor

Background

- IDX184 is a liver-targeted prodrug of 2'-methylguanosine (2'-MeG) monophosphate.
- IDX184 demonstrated potent and selective inhibition of HCV *in vitro*.¹
 - Pan-genotypic activity against HCV types 1, 2, 3 and 4 (mean IC₅₀ values ranging 0.08 µM to 0.29 µM)
- Liver-targeted
 - >95% of absorbed IDX184 is extracted by the liver (portal/systemic ratio >20 in monkey)
 - Low systemic exposures of IDX184 and its nucleoside metabolite, 2'-MeG (humans, monkeys, rats, mice)
 - High levels of the active metabolite, 2'-MeG triphosphate, were measured in the liver in animal models.

IDX184: Liver-Targeted Nucleotide HCV Polymerase Inhibitor

Background (continued)

- High barrier to resistance¹
 - S282T is the signature resistance mutation in replicons.
 - Slow emergence of resistance *in vitro* with low (5%) replicative capacity
- Safe and well tolerated up to 100 mg IDX184 after a single dose in healthy subjects and after 3 doses in HCV-infected subjects.^{2,3}
 - HCV RNA reductions 0.5-0.7 log₁₀ after 3 days of IDX184 monotherapy (25-100 mg)
- The IDX184 program has been placed on clinical hold by the United States Food and Drug Administration after three serious adverse events of elevated liver function tests occurred during a two week drug-drug interaction study of the combination of IDX320 and IDX184 in healthy volunteers.

1. McCarville J, *et al* (2010). 5th International Workshop on Clinical Pharmacology of Hepatitis Therapy. Boston, Massachusetts.
2. Zhou XJ, *et al* (2009). *Journal of Hepatology* 50 Suppl. 1, S351.
3. Lalezari J, *et al* (2009). *Hepatology* 50 Suppl. 4, 228A.

Objectives and Key Eligibility Criteria

IDX184 Phase IIa 14-Day Combination Study

Objectives

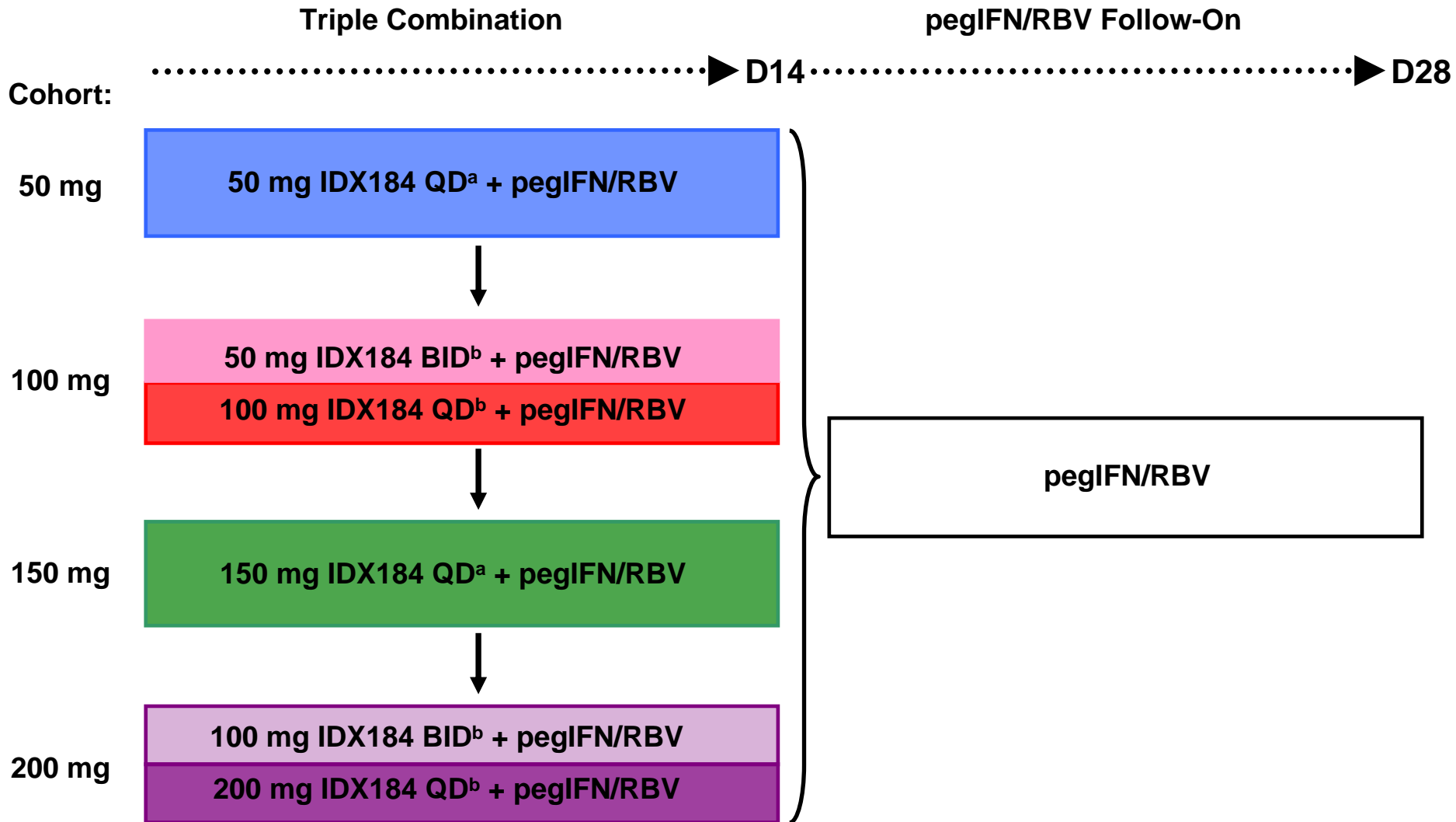
- Evaluate antiviral activity, safety and tolerability of IDX184 + pegIFN/RBV
- Evaluate plasma PK of IDX184 and 2'-MeG
- Guide dose selection for Phase IIb studies

Key Eligibility Criteria

- Treatment-naïve, male and female subjects between 18 and 65 years old with genotype 1, chronic HCV infection without cirrhosis
- BMI ≤ 35 kg/m², HCV RNA ≥ 5 log₁₀ IU/mL, ALT ≤ 3 x ULN

Study Design

IDX184 Phase IIa 14-Day Combination Study



^a16 subjects receive active IDX184:4 subjects receive placebo

^b8 subjects receive active IDX184:2 subjects receive placebo

Demographic and Baseline Parameters

IDX184 Phase IIa 14-Day Combination Study

| Parameter | Placebo + P/R N=16 | IDX184 | | | | | |
|---|--------------------------|---------------------------|---------------------------|---------------------------|----------------------------|----------------------------|---------------------------|
| | | 50 mg QD + P/R N=16 | 50 mg BID + P/R N=8 | 100 mg QD + P/R N=8 | 150 mg QD + P/R N=17 | 100 mg BID + P/R N=8 | 200 mg QD + P/R N=8 |
| Age ^a , yrs | 48 (9) | 51 (10) | 50 (11) | 48 (12) | 48 (12) | 49 (8) | 42 (12) |
| Male/Female, n | 10/6 | 14/2 | 5/3 | 5/3 | 13/4 | 4/4 | 5/3 |
| Race, n (%) | | | | | | | |
| Black | 4 (25) | 5 (31) | 3 (38) | 2 (25) | 3 (18) | 2 (25) | 0 |
| White | 11 (69) | 9 (56) | 5 (63) | 5 (63) | 14 (82) | 6 (75) | 7 (88) |
| Other | 1 (6) | 1 (13) | 0 | 1 (13) | 0 | 0 | 1 (13) |
| BMI ^a , kg/m ² | 28 (3) | 27 (4) | 29 (4) | 29 (4) | 26 (4) | 28 (4) | 29 (4) |
| HCV RNA ^a , log ₁₀ IU/mL | 6.3 (0.5) | 6.1 (0.6) | 6.3 (0.5) | 6.4 (0.6) | 6.4 (0.6) | 6.5 (0.6) | 6.1 (0.5) |
| HCV genotype 1a/1b, n | 13/3 | 13/3 | 7/1 | 7/1 | 16/1 | 7/1 | 5/3 |
| IL28B genotype CC/CT/TT/UK, n | 4/8/2/2 | 4/8/3/1 | 1/6/1/0 | 5/2/1/0 | 5/4/2/6 | 2/4/2/0 | 1/5/0/2 |

^aValues reported as mean (standard deviation)

P/R = pegIFN/RBV; UK=unknown

Antiviral Activity of IDX184 in Combination with pegIFN/RBV

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| 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=16) | -1.5 ± 1.3 | 1 (6%) |
| 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%) |
| 150 mg IDX184 QD + P/R (N=15)* | -4.1 ± 1.2 | 6 (40%) |
| 100 mg IDX184 BID + P/R (N=7)# | -4.3 ± 1.5 | 2 (29%) |
| 200 mg IDX184 QD + P/R (N=8) | -3.7 ± 1.2 | 2 (25%) |

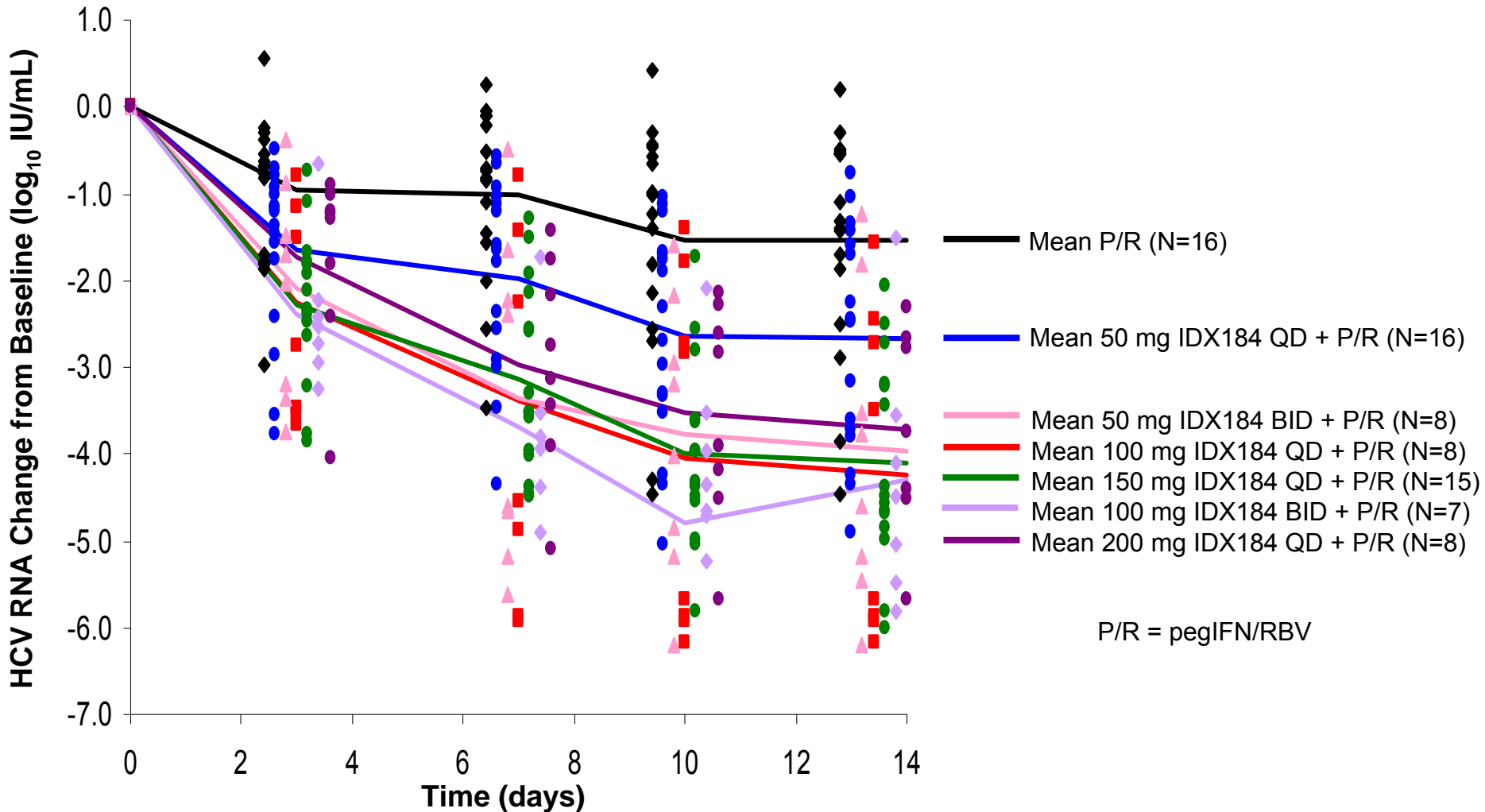
*2 subjects in the 150 mg IDX184 QD group excluded from efficacy analysis due to acute cholecystitis and noncompliance.

#1 subject in the 100 mg IDX184 BID group excluded from efficacy analysis due to noncompliance.

P/R = pegIFN/RBV

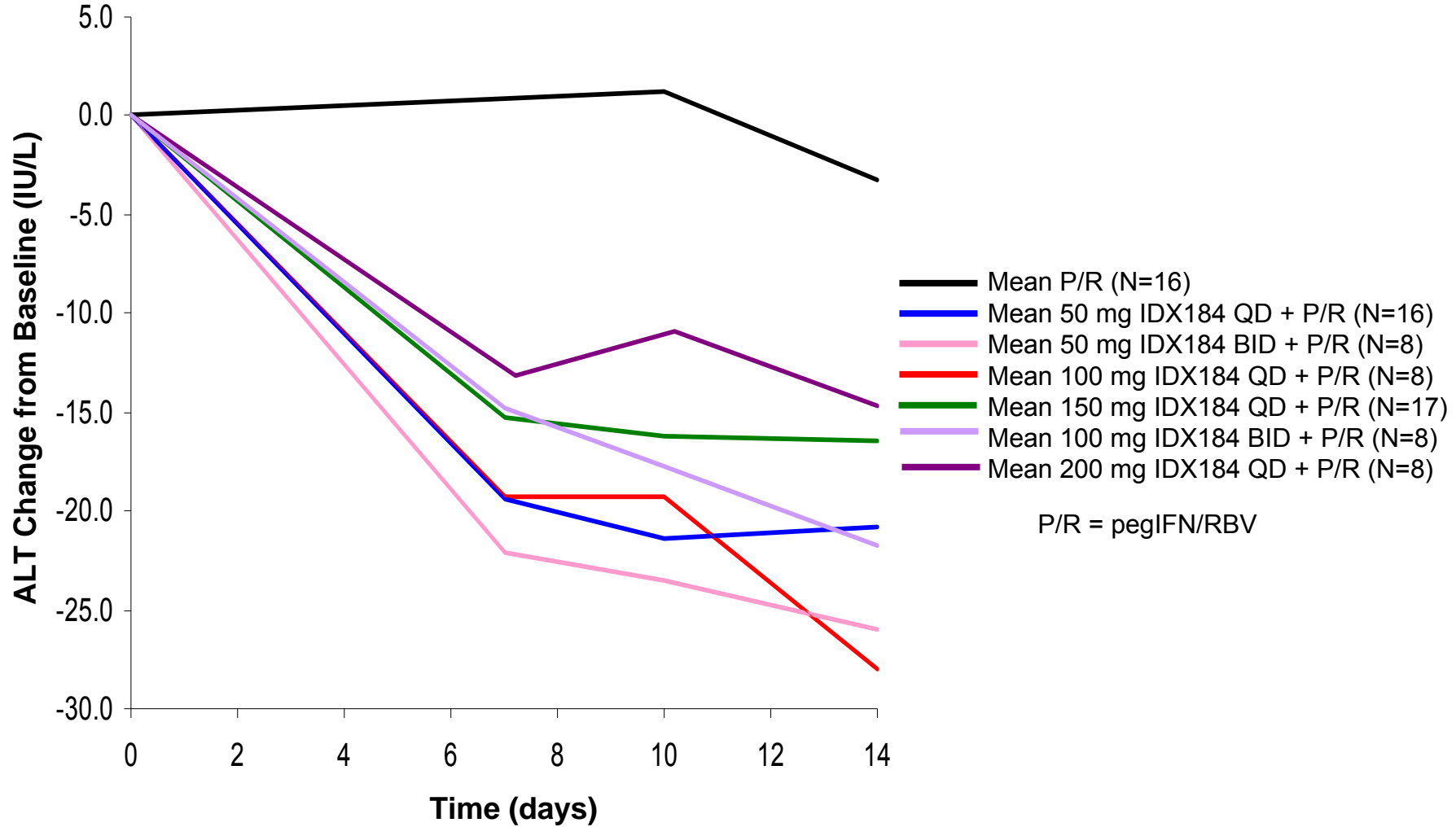
Mean and Individual HCV RNA Changes

IDX184 Phase IIa 14-Day Combination Study



Mean ALT Changes

IDX184 Phase IIa 14-Day Combination Study



Adverse Events through Day 14

IDX184 Phase IIa 14-Day Combination Study

| Adverse Event, n (%) | Placebo + P/R N=16 | IDX184 | | | | | |
|-------------------------|--------------------------|---------------------------|---------------------------|---------------------------|----------------------------|----------------------------|---------------------------|
| | | 50 mg QD + P/R N=16 | 50 mg BID + P/R N=8 | 100 mg QD + P/R N=8 | 150 mg QD + P/R N=17 | 100 mg BID + P/R N=8 | 200 mg QD + P/R N=8 |
| Fatigue | 8 (50) | 9 (56) | 3 (38) | 3 (38) | 9 (53) | 5 (63) | 3 (38) |
| Headache | 6 (38) | 2 (13) | 5 (63) | 2 (25) | 9 (53) | 3 (38) | 5 (63) |
| Nausea | 3 (19) | 4 (25) | 4 (50) | 1 (13) | 4 (24) | 5 (63) | 3 (38) |
| Myalgia | 5 (31) | 7 (44) | 2 (25) | 3 (38) | 2 (12) | 1 (13) | 2 (25) |
| Chills | 5 (31) | 4 (25) | 2 (25) | 2 (25) | 2 (12) | 3 (38) | 2 (25) |
| Pain | 3 (19) | 1 (6) | 2 (25) | 0 | 4 (24) | 1 (13) | 3 (38) |
| Insomnia | 4 (25) | 1 (6) | 1 (13) | 1 (13) | 2 (12) | 2 (25) | 1 (13) |
| Irritability | 2 (13) | 1 (6) | 0 | 3 (38) | 2 (12) | 1 (13) | 1 (13) |

>10% of subjects across cohorts

- 1 SAE occurred during the 14 day IDX184 treatment period
 - A subject in the 150 mg IDX184 QD group experienced acute cholecystitis. Ultrasound showed echogenic debris within gallbladder, a thickened wall and pericholecystic fluid/edema → cholecystectomy performed. The investigator considered the event possibly related to pegIFN/RBV.

Graded ALT, Creatinine and Hemoglobin through Day 14

IDX184 Phase IIa 14-Day Combination Study

| n (%) | Placebo + P/R N=16 | IDX184 | | | | | |
|---------------------|--------------------------|---------------------------|---------------------------|---------------------------|----------------------------|----------------------------|---------------------------|
| | | 50 mg QD + P/R N=16 | 50 mg BID + P/R N=8 | 100 mg QD + P/R N=8 | 150 mg QD + P/R N=17 | 100 mg BID + P/R N=8 | 200 mg QD + P/R N=8 |
| ALT ↑ | | | | | | | |
| Grade 1/2 | 4 (27) | 1 (7) | 0 | 1 (13) | 0 | 0 | 0 |
| Grade 3/4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Creatinine ↑ | | | | | | | |
| Grade 1/2 | 0 | 0 | 1 (13) | 1 (13) | 0 | 0 | 0 |
| Grade 3/4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hemoglobin ↓ | | | | | | | |
| Grade 1/2 | 5 (31) | 3 (19) | 1 (13) | 1 (13) | 1 (6) | 0 | 3 (38) |
| Grade 3/4 | 0 | 0 | 0 | 0 | 1 (6) | 0 | 0 |

- Graded ALT, creatinine and hemoglobin abnormalities were comparable across treatment groups.

Grade 3/4 Laboratory Abnormalities through Day 14

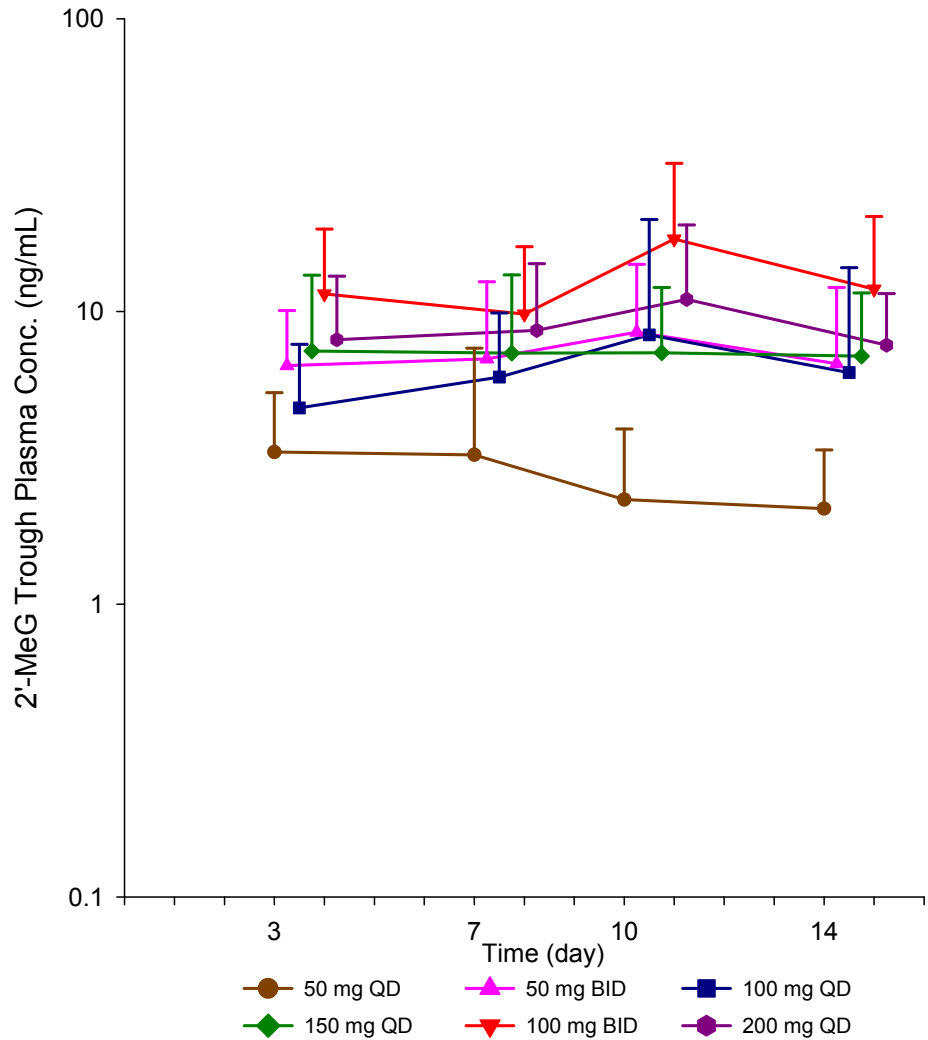
IDX184 Phase IIa 14-Day Combination Study

| Laboratory Parameter, n (%) | IDX184 | | | | | | |
|--|-----------------------|------------------------|------------------------|------------------------|-------------------------|-------------------------|------------------------|
| | Placebo + P/R N=16 | 50 mg QD + P/R N=16 | 50 mg BID + P/R N=8 | 100 mg QD + P/R N=8 | 150 mg QD + P/R N=17 | 100 mg BID + P/R N=8 | 200 mg QD + P/R N=8 |
| Hemoglobin ≤ 7.4 g/dL | 0 | 0 | 0 | 0 | 1 (6) | 0 | 0 |
| Neutrophils $\leq 749/\text{mm}^3$ | 3 (19) | 3 (19) | 1 (13) | 0 | 0 | 1 (13) | 0 |
| Prothrombin time $\geq 1.51 \times \text{ULN}$ | 0 | 0 | 0 | 0 | 1 (6) | 0 | 0 |
| Triglycerides ≥ 751 mg/dL | 0 | 0 | 0 | 1 (13) | 0 | 0 | 0 |

- Consistent with pegIFN/RBV administration
- No discernable patterns across treatment groups

Mean (+SD) Plasma C_{trough} of 2'-MeG

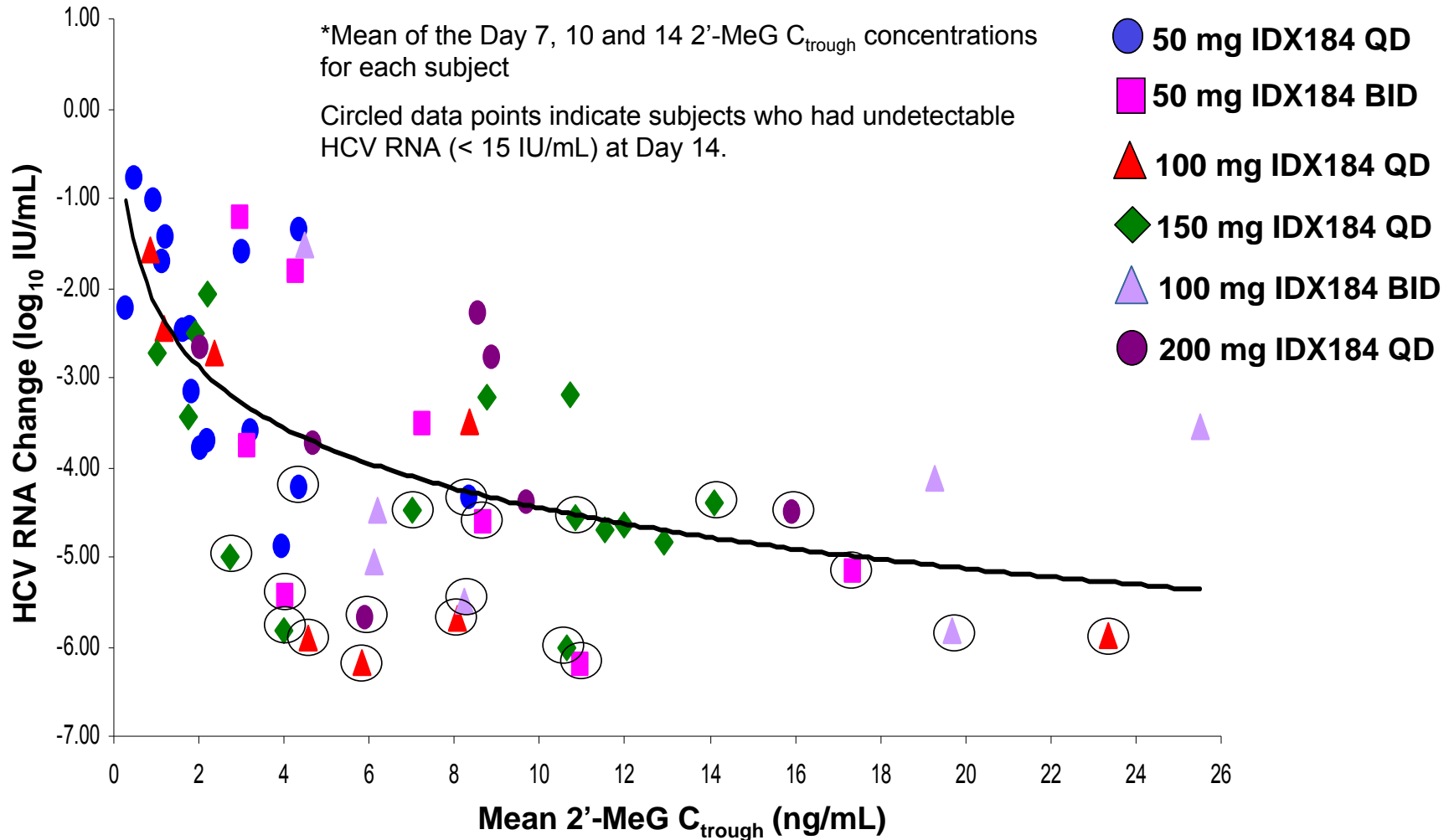
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- 2'-MeG C_{trough} increased with increasing doses
- 2'-MeG C_{trough} consistent between Day 7 and Day 14

E_{\max} Model - HCV RNA Decline at Day 14 and 2'-MeG C_{trough}^*

IDX184 Phase IIa 14-Day Combination Study



- E_{\max} modeling confirmed a PK/PD relationship between the HCV viral load decline at Day 14 and mean 2'-MeG C_{trough} ($p < 0.0001$).

Conclusions

IDX184 Phase IIa 14-Day Combination Study

- IDX184 demonstrated potent antiviral activity when combined with pegIFN/RBV.
- Approximate 4 log HCV RNA reduction with up to 50% of subjects achieving undetectable HCV RNA by Day 14 with IDX184 doses of 100 mg; antiviral activity plateaued at doses \geq 100 mg.
- No S282T mutations were detected by population sequencing during the 14 days of treatment.
- Side effect profile of IDX184 in combination with pegIFN/RBV was consistent with the known side effect profile of pegIFN/RBV.
- PK profile supports once daily dosing.
- IDX184 doses of 50 mg QD and 100 mg QD proposed for further evaluation in long-term clinical studies.

Acknowledgements

IDX184 Phase IIa 14-Day Combination Study

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