Antiviral Activity and Safety of INX-08189, a Nucleotide Polymerase Inhibitor, Following 7-Days of Oral Therapy in Naïve Genotype-1 HCV Patients

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Introduction

INX-08189 is a novel guanosine nucleotide polymerase inhibitor that has shown significant antiviral activity against HCV in preclinical replicon studies (EC_{50}=10 nM). In a healthy volunteer Phase 1a study, once daily doses of INX-08189 ranging from 3 mg to 100 mg were shown to be well tolerated.

Methods

In these multicenter, double-blind, placebo-controlled, multiple-dose studies, 80 subjects were enrolled in 8 cohorts and randomized 8:2 to receive either 9 mg, 25 mg, 50 mg, 100 mg, or 200 mg once daily for 7 days or placebo. An additional cohort that received 50 mg on day 1 followed by 9 mg on days 2-6 of INX-08189 or placebo daily was also evaluated. In order to confirm the preclinical antiviral synergy observed with INX-08189 in combination with RBV, INX-08189 (9 and 25 mg) was given with RBV for seven days in 2 additional cohorts.

Results

All doses of INX-08189 resulted in a significant reduction in median plasma HCV RNA levels compared to placebo. Figures 2A and 2B show the decline in HCV RNA levels from baseline at days 3 and 7 of monotherapy. 200 mg of INX-08189 taken once daily resulted in a median drop of -4.25 logs from baseline. When RBV was added to 25 mg of INX-08189, the median drop was 0.5 logs greater than monotherapy. INX-08189 was well-tolerated and no increase in severity or type of AE's was observed with increasing doses. There was one SAE in the placebo + RBV cohort (atrial fibrillation). The most common adverse event was headache. Among the 6 INX-08189 monotherapy cohorts, there were no treatment-emergent adverse events reflecting laboratory abnormalities > grade 1. In the 25 mg INX-08189 + RBV cohort there was one grade 3 lab abnormality (decrease in hemoglobin). Among all 8 cohorts there were no treatment-emergent ECG abnormalities among INX-08189-treated subjects.

Table 1: Pharmacokinetics

PK Parameter Mean (CV%)	9 mg N = 7	9 mg + RBV N=7	25 mg N = 8	25 mg + RBV N=7	50 mg N = 8	100 mg N=8
T_{max} (hr) (min, max)	4.2 (3.00, 5.00)	4.1 (3.00, 5.00)	4.4 (4.00, 5.00)	4.3 (3.98, 5.00)	3.75 (3.00, 5.00)	4.3 (3.00, 8.00)
C_{max} (ng/mL)	5.81 (44.8)	5.08 (45.7)	23.3 (59.2)	13.1 (58.2)	25.7 (50.1)	39.7 (33.9)
AUC_{0-24} (ng•hr/mL) (%CV)	54.88 (27.9)	43.3 (54.8)	174.04 (38.2)	100.71 (37.9)	217.16 (34.2)	404.9 (43.4)
$t_{1/2}$ (hr) (%CV)	6.4 (79.7)	3.43 (44.7)	23.5* (77.3)	9.03 (46.1)	29.6** (29.9)	36.2*** (67.4)

*$T_{1/2}$ was variable and ranged from 3.10 to 60.3
**$T_{1/2}$ ranged from 18.8 to 43.0
***$T_{1/2}$ was variable and ranged from 8.4 to 68.9

Table 2: Study Population Demographic and Baseline Characteristics

Attribute	PBO[1] N = 10 n (%)	9 mg N = 8 n (%)	25 mg N = 8 n (%)	50mg/ 9mg N = 8 n (%)	50 mg N = 8 n (%)	100 mg N = 8 n (%)	200 mg N = 8 n (%)	PBO + RBV N = 4 n (%)	9 mg + RBV N = 8 n (%)	25 mg + RBV N = 8 n (%)
Age (median yrs)	47.0 (25, 38)	47.5 (29, 58)	54.5 (32, 64)	51.0 (37, 58)	46.5 (28, 60)	46.5 (28, 60)	39.9 (20, 54)	46.0 (41, 53)	46.0 (31, 61)	42.5 (29, 52)
Sex (n % male)	7 (30.0)	4 (50.0)	7 (87.5)	6 (75.0)	7 (87.5)	7 (87.5)	6 (75.0)	4 (100)	7 (87.5)	8 (100)
Race Caucasian	7 (70.0)	6 (75.0)	4 (45.0)	4 (50.0)	5 (62.5)	7 (87.5)	7 (87.5)	3 (75.0)	5 (62.5)	5 (62.5)
African American	3 (30.0)	2 (25.0)	4 (50.0)	3 (37.5)	3 (37.5)	1 (12.5)	1(12.5)	1 (25.0)	3 (37.5)	3 (37.5)
Native American	0	0	0	1 (12.5)	0	0	0	0	0	0
HCV Genotype GT1a:1b	9:1	8:0	6:2	8:0	8:0	7:1	7:1	3:1	6:2	7:1
Mean baseline HCV RNA log10	6.33 (5.53-7.00)	6.29 (5.62, 7.09)	6.35 (5.11, 6.86)	6.15 (3.85, 7.20)	6.09 (5.10, 6.75)	6.35 (5.12, 7.01)	6.35 (5.49, 6.70)	6.02 (5.04, 6.78)	6.48 (5.49, 7.24)	6.15 (5.68, 6.80)
IL28B CC allele	1 (10.0)	2 (25.0)	1 (12.5)	4 (50.0)	1 (12.5)	1 (12.5)	4 (50.0)	1 (25.0)	1 (12.5)	2 (25.0)
Liver Fibrosis Present	10	6	5	8	6	5	U[2]	4	6	5

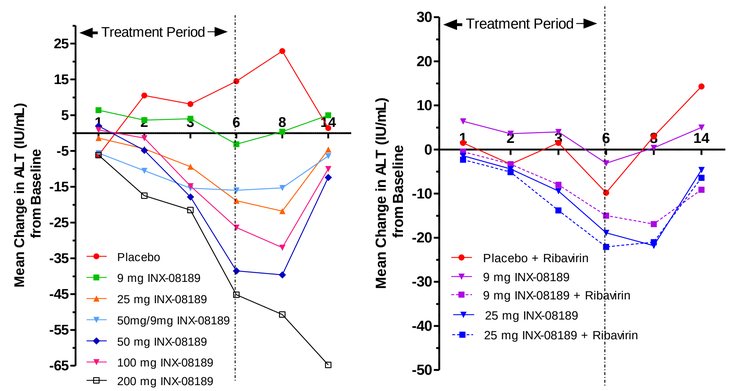
[1]Does not reflect 2 placebo subjects from 200mg cohort
[2]Unknown at present

Table 3: Clinical Safety

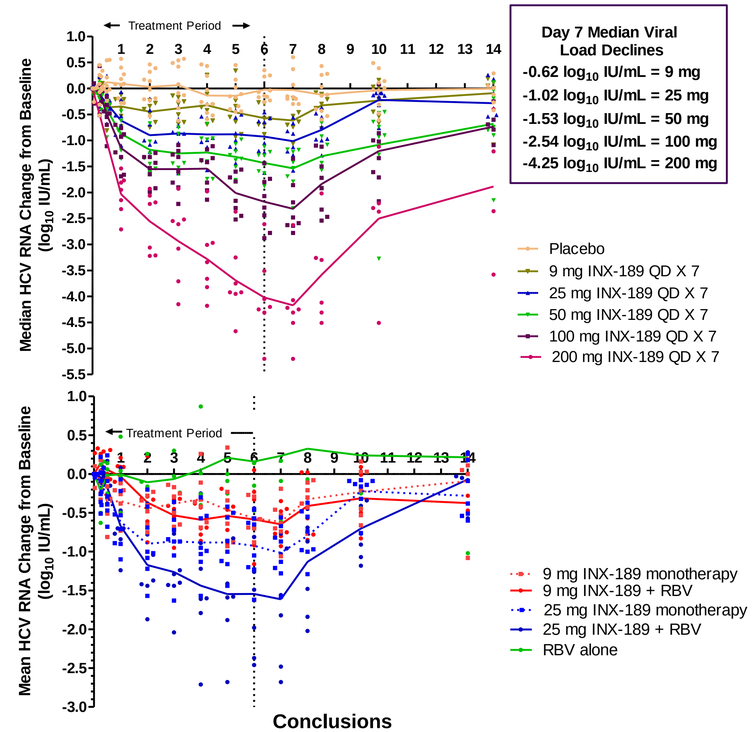
Preferred Term	PBO N = 12 n (%)	9 mg N = 8 n (%)	25 mg N = 8 n (%)	50mg/ 9mg N = 8 n (%)	50mg N = 8 n (%)	100 mg N = 8 n (%)	200 mg N = 8 n (%)	PBO + RBV N = 4 n (%)	9mg + RBV N = 8 n (%)	25mg + RBV N = 8 n (%)
# subjects with any TEAE	6 (50.0)	4 (50.0)	2 (25.0)	2 (25.0)	6 (75.0)	3 (37.5)	3 (37.5)	2 (50.0)	4 (50.0)	1 (12.5)
Headache	2 (16.7)	1 (12.5)	0	1 (12.5)	3 (37.5)	1 (12.5)	2 (25.0)	0	0	1 (12.5)
Nausea	0	1 (12.5)	0	0	0	1 (12.5)	0	1 (25.0)	1 (12.5)	0
Vomiting	0	0	0	0	0	1 (12.5)	0	0	2 (25.0)	0
Abdominal pain	0	0	0	0	1 (12.5)	1 (12.5)	0	0	1 (12.5)	0
Diarrhea	0	1 (12.5)	1 (12.5)	0	0	1 (12.5)	1 (12.5)	0	0	0
Nasal congestion	0	1 (12.5)	0	1 (12.5)	0	0	0	0	1 (12.5)	0

- No serious adverse events (SAE) reported in INX-189 dosed subjects; 1 SAE in the placebo/RBV cohort (atrial fibrillation on 7th day of dosing)

Figure 1: Mean ALT Values Change from Baseline



Figures 2A: (monotherapy) & 2B (+RBV): Mean HCV RNA Change from Baseline



Conclusions

- INX-08189 was generally well tolerated at all dose levels
- INX-08189 produced a dose dependent decrease in HCV RNA levels and achieved a median reduction of -4.25 logs from baseline at the highest monotherapy dose level of 200 mg QD
- Combination treatment of RBV + 25 mg of INX-08189, resulted in viral load reduction 0.5 logs greater than 25 mg INX-08189 monotherapy, corroborating *in vitro* replicon results which demonstrated INX-08189 synergy with RBV
- These data support the initiation of a Phase II study of longer dosing duration with INX-08189