

A Study of the Safety and Pharmacokinetics of Single Ascending Oral Doses of INX-08189, a Nucleotide Polymerase Inhibitor, in Healthy Subjects

A Barry¹, J Patti¹, M Matson², B Boehlecke³, E Wenzel¹, H Pentikis⁴, J Alam¹, and G Henson¹

¹Inhibitex, Inc. Alpharetta, GA, ²Prism Research, St. Paul, MN, ³Rho Inc., Chapel Hill, NC, ⁴SAJE Consulting, Baltimore, MD



Background

INX-08189 is a highly potent phosphoramidate analog of the nucleoside O6-methyl-2'-C-methyl guanosine that has recently completed a Phase 1b clinical study in chronic HCV genotype 1 treatment-naïve subjects. INX-08189 has previously been shown to exhibit pan-genotypic activity and a high genetic barrier to resistance *in vitro*. The EC₉₀ for INX-08189 in the genotype 1a, 1b, and 2a replicon assays was 42 nM, 38 nM, and 7 nM, respectively. Pharmacodynamic studies in rats and primates indicated that levels of the triphosphate exceeding the EC₉₀ were achieved for ≥ 24 hours post single oral dosing at human equivalent doses of 100 mg. In these animal studies liver triphosphate levels were proportional to nucleoside metabolite plasma concentrations (INX-08032) which were used as a surrogate to study INX-08189 PK in the clinic.

Methods

This was a single center, sequential-cohort, double-blind, placebo-controlled, single-ascending-dose (SAD) study. Subjects were assigned sequentially to the following 5 SAD cohorts: 3, 9, 25, 50, and 100 mg. Subjects were randomized after cohort assignment to receive INX-08189 or placebo in a 6:2 ratio. The effect of a standard high-fat meal on the absorption of INX-08189 was also evaluated at the 25 mg dose in the same cohort of subjects who received this dose without food. Subjects were confined in a Phase I unit for 12 hours before dosing and for 24 hours after dosing for observation and PK sampling. Safety was monitored by physical examinations (PEs), vital signs (VS), clinical laboratory tests, electrocardiograms (ECGs), and adverse event (AE) assessments.

Results

- INX-08032 was rapidly eliminated from plasma.
- Renal elimination of INX-08032 accounted for approximately 7 to 12% of the INX-08189 dose.
- Concomitant administration of INX-08189 with food significantly reduced circulating concentrations of INX-08032.
- INX-08032 C_{max} and exposure increased in a dose-proportional manner.
- No dose-related trends in AE's and all AE's were mild or moderate
- No dose-related serious adverse events.
- The most common AE's were headache, presyncope, ecchymosis, and nasal congestion.
- AE's assessed to be drug-related were 1 pyrexia (9 mg), 2 headaches (3 & 9 mg), 1 flushing (50 mg), and 1 dyspepsia (50 mg).
- No treatment-emergent changes in ECG or grade 2 or higher laboratory values were observed with the exception of several elevated cholesterol values in subjects with elevated total cholesterol at baseline.

Figure 1 – Plasma Concentration of INX-08032 (2'-C-Methyl Guanosine metabolite) Following INX-08189 Oral Dose Administration in Fasted Subjects

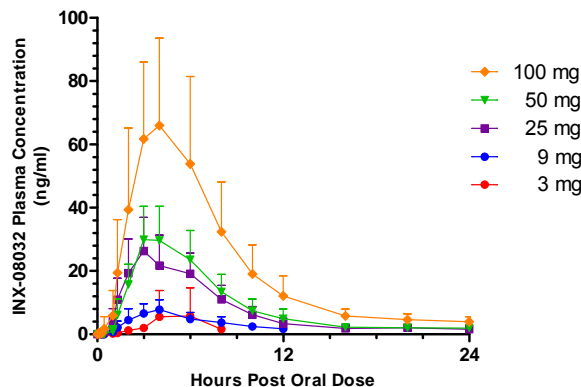


Table 1 – Summary Pharmacokinetics of INX-08032 (2'-C-Methyl Guanosine metabolite) by Cohort Following Single Oral Dose Administration of INX-08189

	3 mg Fasted (N=6)		9 mg Fasted (N=6)		25 mg Fasted (N=6)		25 mg Fed (N=4)		50 mg Fasted (N=6)		100 mg Fasted (N=8)	
PK Param.	Mean	% CV	Mean	% CV	Mean	% CV	Mean	% CV	Mean	% CV	Mean	% CV
C _{max} (ng/mL)	2.09	25.4	8.82	34.7	27.22	36.3	12.64	30.7	32.49	35.9	68.24	41.5
T _{max} (hr) ^b	3.50	3.0-6.0	8.04	5.73-13.17	3.0	3.0-6.0	6.0	3.0-8.0	3.5	3.0-4.0	4.0	3.0-6.0
AUC ₀₋₂₄ (ng•hr/mL)	ND ^a	ND	65.36	24.90	218.6	8.4	90.74	28.7	208.2	40.7	507.2	42.6
AUC _{0-last} (ng•hr/mL)	6.86	64.4	39.48	48.8	162.1	39.8	73.55	40.4	225.4	53.4	588.1	44.1
AUC _{0-inf} (ng•hr/mL) ^c	ND	ND	66.20	23.5	228.9	8.5	91.62	28.0	199.7	47.8	675.2	39.5
t _{1/2} (hr)	ND	ND	3.48	35.1	6.02	99.9	2.92	24.0	6.75	105.3	31.61	69.7

^a ND = not determined because of insufficient data, ^b median, minimum – maximum, ^c Number of subjects for which AUC_{0-inf} could be calculated: 9 mg, n=2; 25 mg fasted/fed, n=3; 50 mg, n=4; 100 mg, n=7.)

Figure 2 – Plasma AUC's of INX-08189 and INX0832

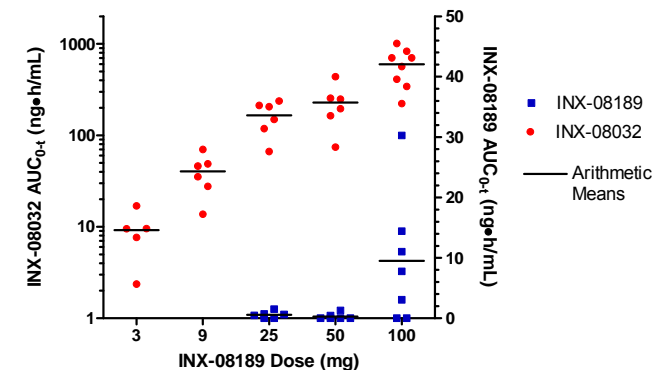


Table 2 – Adverse Events by Treatment

	Placebo Fasted (N=10)	3 mg Fasted (N=6)	9 mg Fasted (N=6)	25 mg Fasted (N=6)	25 mg Fed (N=4)	50 mg Fasted (N=6)	100 mg Fasted (N=8)
# AE's	3	4	5	1	0	15 ^a	6
# Drug-Related AE's	0	2	1	0	0	2	0
# (%) of Subjects with any AE	3 (30)	3 (50)	4 (67)	1 (17)	0	5 (83)	3 (38)

^a One subject with SAE unrelated to study drug exhibited 6/15 AE's in this cohort.

Conclusions

- INX-08189 exhibited a favorable safety profile at all doses evaluated in this study.
- INX-08189 plasma concentrations were low and sporadic suggesting rapid metabolism to the active triphosphate.
- Doses ≥ 9 mg exhibited plasma metabolite exposures that would be expected to indicate liver triphosphate levels in the antiviral range.
- Additional clinical studies to evaluate multiple ascending doses are warranted to further evaluate the pharmacokinetics and safety of INX-08189