

IDX375, A Novel Non-nucleoside HCV Polymerase Inhibitor: Safety, Tolerability and Pharmacokinetics (PK) in a Phase I Study

J. v.d. Wetering de Rooij, X.J. Zhou, M.F. Temam, J. Molles, J. Chen, K. Pietropaolo, J.Z. Sullivan-Bólyai and D. Mayers

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IDX375 Background

- Palm-binding non-nucleoside HCV polymerase inhibitor
- Potent and selective
 - Low nanomolar potency *in vitro*, with 3-fold more activity in HCV genotype 1b ($EC_{50}=1.2$ ng/mL) vs. genotype 1a replicon
 - No inhibition of human cellular DNA and RNA polymerases
- Favorable pharmacokinetic profile in several species
- High liver:plasma ratios in rodents
- Limited potential for drug-drug interactions
- 2-week toxicology program in both mice and monkeys supports initial human trials
- Solid dosage formulation developed to optimize drug exposure (minimal differences between C_{max} and C_{min})

IDX375 Choline Salt Phase I Study

Study Design

- Objectives: safety and tolerability, PK
- Population: healthy male volunteers
- Randomized, double-blind, placebo-controlled, sequential group, dose-escalation
- Dosing after a standard meal
- Safety review between ascending dose cohorts

N (active:placebo)	IDX375 Administration x 1 Day
6:2	25 mg IDX375 in solution
6:2	50 mg IDX375 in solution
6:2	1 x 100 mg IDX375 capsule
6:2	2 x 100 mg IDX375 capsules
6:2	2 x 100 mg IDX375 capsules BID

- Plasma and urine levels of IDX375 were quantified using a validated LC-MS/MS methodology.

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Baseline Demographics

	IDX375					
	Placebo N=10	25 mg N=6	50 mg N=6	100 mg N=6	200 mg N=6	200 mg BID N=6
Mean age (SD), yrs	41.0 (19.1)	42.0 (16.7)	45.8 (20.1)	45.8 (15.9)	51.5 (17.6)	38.3 (16.8)
Sex, n						
Male	10	6	6	6	6	6
Race, n						
Asian	0	1	0	1	0	0
White	10	5	6	5	5	6
Other	0	0	0	0	1	0
Mean height (SD), cm	181.9 (7.9)	178.8 (7.3)	180.2 (6.7)	180.3 (7.1)	180.5 (11.4)	187.0 (3.4)
Mean weight (SD), kg	84.8 (11.1)	86.9 (7.2)	87.7 (11.4)	80.9 (12.0)	77.7 (15.3)	80.8 (9.2)
Mean BMI (SD), kg/m ²	25.3 (2.8)	26.9 (2.7)	26.5 (3.0)	24.6 (2.6)	23.5 (3.0)	22.6 (2.7)

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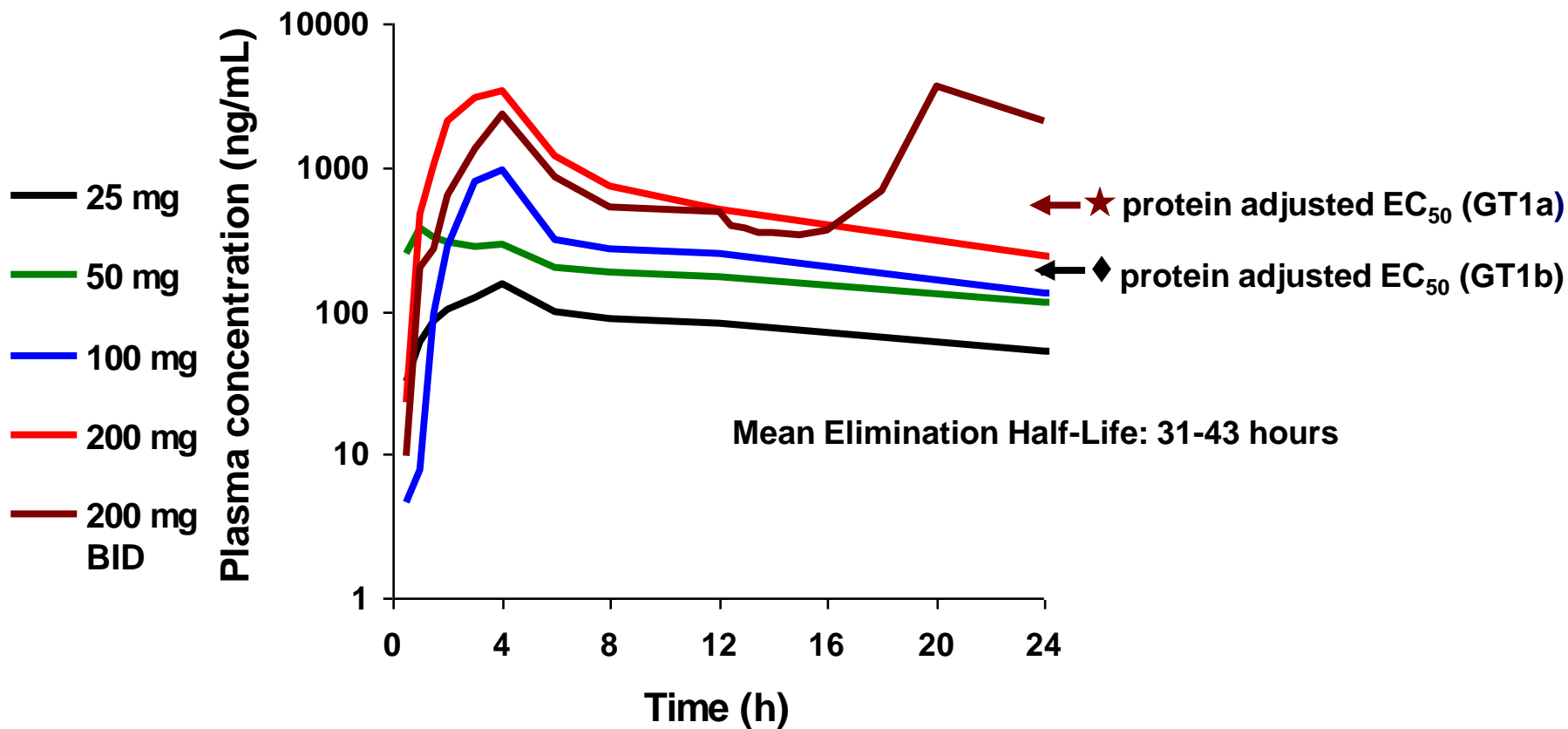
Safety Summary

AE Term, n	Placebo N=10	IDX375				
		25 mg N=6	50 mg N=6	100 mg N=6	200 mg N=6	200 mg BID N=6
Diarrhea	0	0	1	0	1	1
Flatulence	0	0	0	0	1	0
Headache	1	0	0	0	0	0
Nasal Congestion	1	0	0	0	0	0
Pollakiuria	0	0	0	0	1	0
Polyuria	0	0	1	0	0	0
Toothache	1	0	0	0	0	0

- No SAEs, premature discontinuations or dose-limiting toxicities
- All AEs mild
- No relationship to dose
- No patterns in laboratory parameters
- No clinically significant ECG abnormalities

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Dose-Proportional Pharmacokinetics



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Pharmacokinetic Parameters of IDX375 Choline Salt

Dose (mg)	C _{max} (ng/mL)	T _{max} (h)	AUC _{0-∞} (μg*h/mL)	t _{1/2} (h)	C _{24h} (ng/mL)
25	163 (45)	4 (2-4)	5.2 (1.2)	42.3 (8.6)	53 (9.7)
50	415 (76)	1 (1-4)	12.0 (3.2)	43.3 (13.8)	113 (32.8)
100	980 (779)	4 (4-6)	13.9 (5.8)	32.6 (6.4)	133 (44.7)
200	3832 (2895)	4 (3-6)	29.4 (15.7)	32.5 (7.2)	239 (138)
200 BID AM	2382 (1342)	4 (3-6)	46.8 (7.4) [#]	31.0 (7.7) ^{\$}	494 (135) ^{&}
200 BID PM	4120 (801)	8 (8-12)			2095 (1074) ^{&}

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

[#]based on daily dose; ^{\$}PM dose; [&]C_{12h}

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Summary and Conclusions

- At tested doses, IDX375 choline salt was generally safe and well-tolerated during this one-day study.
 - Mild diarrhea in 3/30 subjects
 - No significant laboratory abnormalities
- PK supports QD or BID dosing with C_{\min} above protein-adjusted EC_{50} for 200 mg QD and BID dosing.
- Plasma exposure was dose-proportional and urinary excretion accounted for < 0.1 % of administered dose.
- This Phase I study in healthy volunteers is being extended with higher single and multiple doses of a free acid form of IDX375 due to improved stability profile of the drug product.

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