

IDX320, A Novel Macrocyclic HCV Protease Inhibitor: Safety, Tolerability and Pharmacokinetics (PK) in a Phase I Clinical Study

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IDX320 Background

- Potent non-covalent macrocyclic inhibitor of NS3/4A protease enzymes with multi-genotypic coverage
 - Genotypes 1a, 1b, 2a and 4a (0.8 to 1.9 nM IC₅₀) and genotype 3a (23 nM IC₅₀)
- Tight binding to enzyme (K_D of 0.8 nM) with a dissociation half-life of >9 hrs
- No inhibition of 9 human cellular proteases
- Limited potential for drug-drug interactions
- PK profile supports 200 to 400 mg once-daily dosing in man
- High safety margin in 28-day toxicology studies in mice and monkeys

IDX320 Phase I Study

Study Design

- Objectives: safety and tolerability, PK, food effect
- Population: healthy male volunteers
- Randomized, double-blind, placebo-controlled, sequential groups
- Safety review between ascending dose cohorts

N (active:placebo)	IDX320 Administration
6:2	50 mg X 1 day (fed)
6:2	100 mg X 1 day (fed)
6:2	200 mg X 1 day (fed)
6:2	400 mg X 1 day (fed)
6:2	400 mg X 1 day (fasted)
6:2	400 mg X 3 days (fed)

- Plasma levels of IDX320 were quantified using a validated LC-MS/MS methodology.

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Baseline Demographics

	Single Dose IDX320						3-Day Dosing IDX320	
	Placebo N=10	50 mg N=6	100 mg N=6	200 mg N=6	400 mg N=6	400 mg fasted N=6	Placebo N=2	400 mg N=6
Mean age (SD), yrs	43.0 (14.9)	27.0 (9.9)	36.5 (20.6)	29.2 (15.9)	41.7 (15.7)	37.8 (17.4)	44.5 (27.6)	53.3 (12.0)
Male/Female	10/0	6/0	6/0	6/0	6/0	6/0	2/0	6/0
Race, n								
Black	0	0	0	1	0	0	0	0
White	10	5	6	4	5	6	1	6
Other	0	1	0	1	1	0	1	0
Mean height (SD), cm	179.7 (7.0)	179.5 (6.2)	179.8 (5.0)	178.0 (9.0)	180.7 (3.7)	182.5 (7.3)	178.5 (12.0)	183.3 (8.9)
Mean weight (SD), kg	78.3 (5.4)	69.7 (11.6)	81.1 (9.7)	81.8 (8.1)	82.0 (11.2)	75.5 (7.9)	79.4 (8.5)	84.5 (9.2)
Mean BMI (SD), kg/m ²	24.1 (3.0)	21.3 (2.5)	25.1 (4.0)	25.6 (2.3)	24.9 (2.9)	22.3 (2.5)	24.5 (0.6)	25.0 (5.0)

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Adverse Events

	Single Dose IDX320						3-Day Dosing IDX320	
	Placebo N=10	50 mg N=6	100 mg N=6	200 mg N=6	400 mg N=6	400 mg fasted N=6	Placebo N=2	400 mg N=6
Flatulence	1	2	0	0	2	0	1	0
Headache	0	1	1	3	0	0	2	1
Abdominal Pain	1	0	2	0	0	0	0	0
Diarrhea	1	0	0	0	1	0	1	1
Back Pain	0	0	0	1	0	1	0	1
Catheter Site Reaction	0	0	0	0	1	1	0	0
Hyperhidrosis	0	0	0	1	1	0	0	0
Musculoskeletal Stiffness	0	2	0	0	0	0	0	0
Myalgia	0	2	0	0	0	0	0	0
Oropharyngeal Pain	1	0	1	0	0	0	0	0
Urinary Frequency	0	0	0	0	2	0	0	0
Somnolence	0	0	1	0	0	1	0	0
Puncture Site Reaction	1	0	0	0	1	0	0	0

Adverse events in > 1 subject.

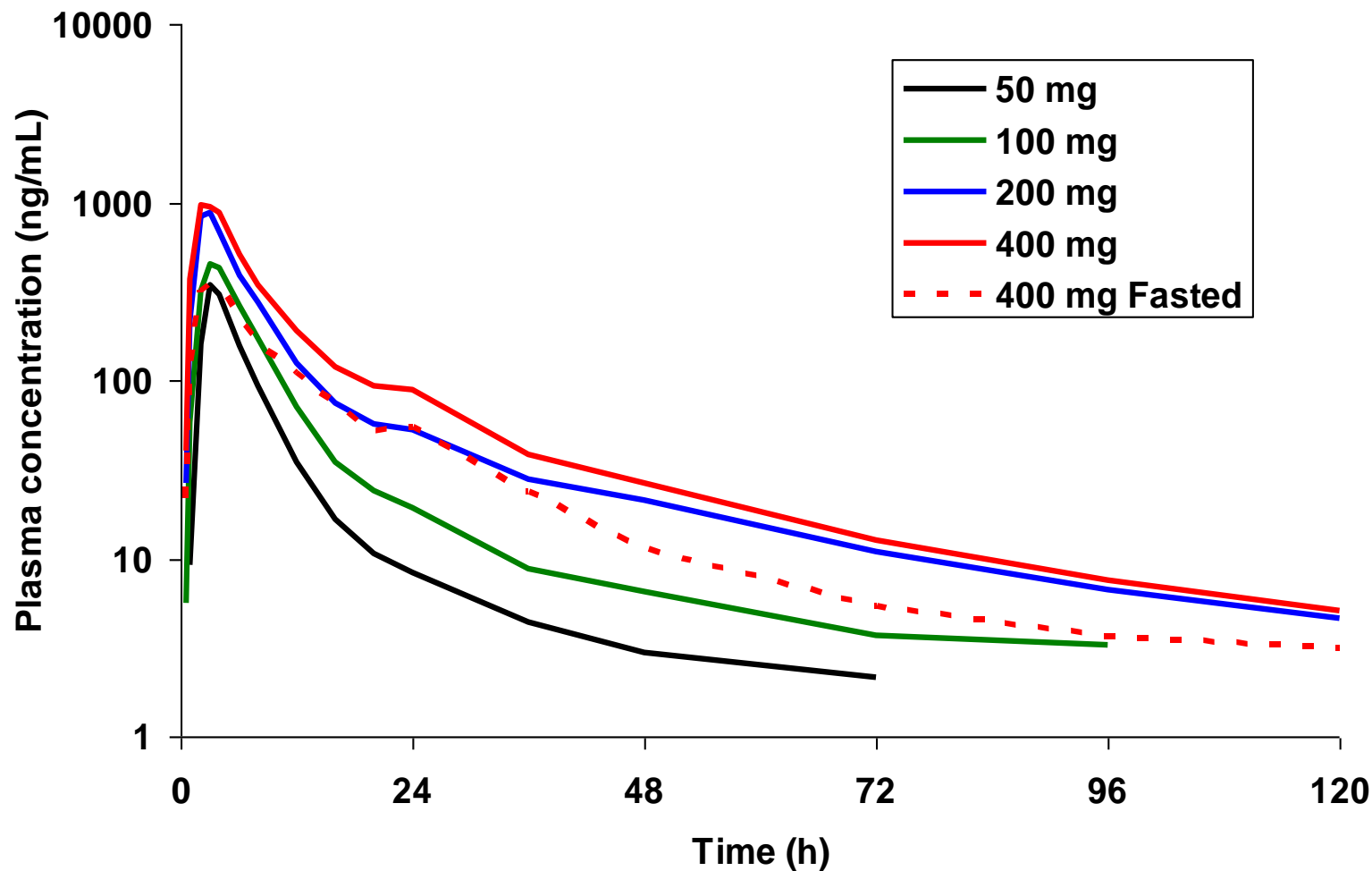
IDX320 Phase I Study

Safety Summary

- No premature discontinuations, serious adverse events, dose-limiting toxicities
- All adverse events mild
- No clinically significant laboratory abnormalities
- No discernable patterns in adverse events, laboratory abnormalities, vital signs or ECG parameters between the IDX320 groups and placebo

IDX320 Phase I Study

Mean Plasma Concentrations of IDX320: Single Dose



IDX320 Phase I Study

Pharmacokinetic Parameters of IDX320: Single Dose

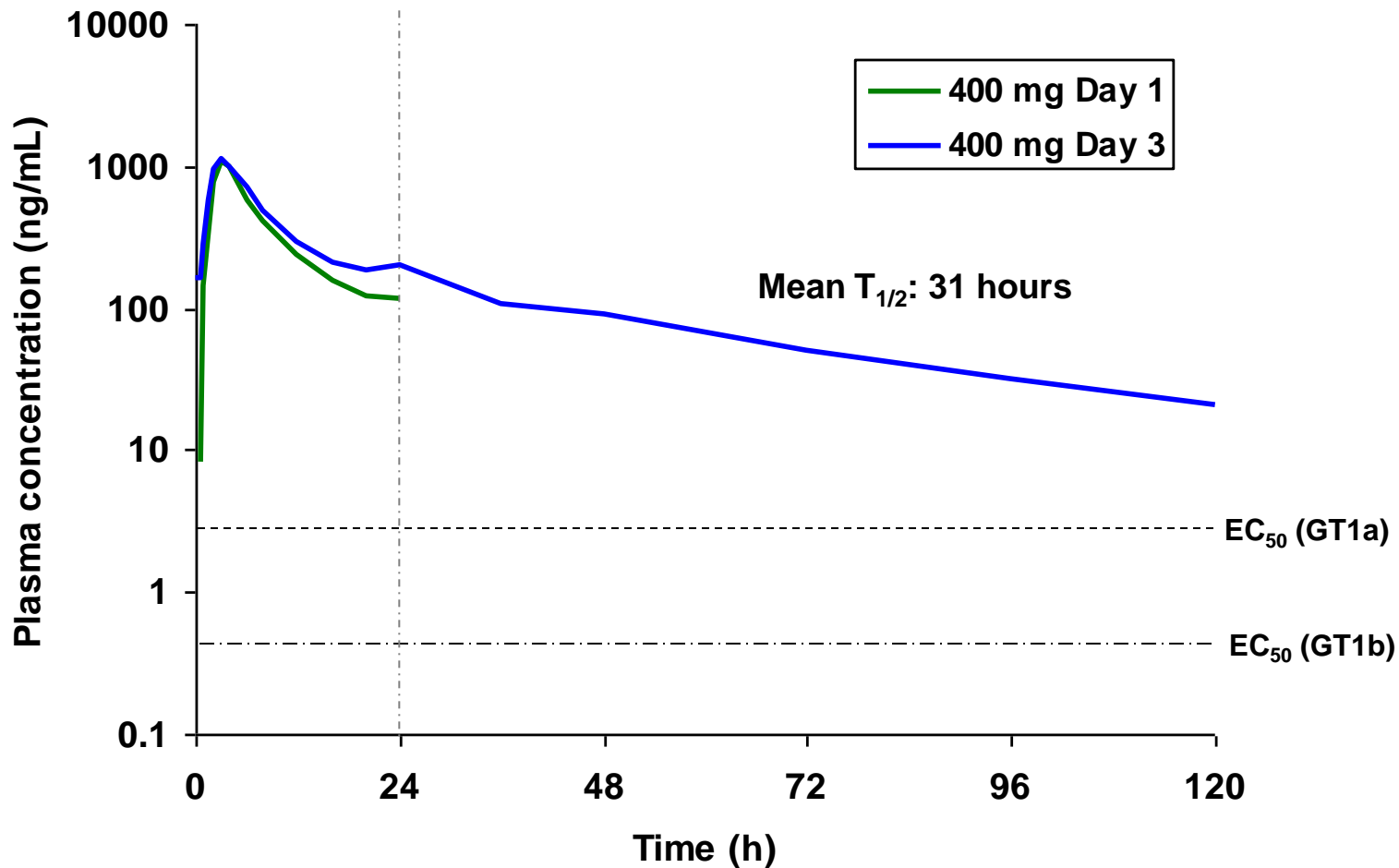
Dose (mg)	C _{max} (ng/mL)	T _{max} (h)	AUC _{0-∞} (ng*h/mL)	T _{1/2} (h)	C _{24h} (ng/mL)
50	346±86.8	3.0 (3.0-3.0)	2022±744	12.7±6.3	8.4±4.8 (2.0-16)
100	467±72.1	3.0 (2.0-4.0)	3543±1013	24.0±7.2	19±8.7 (9.7-35)
200	982±463	3.0 (2.0-3.0)	7239±2927	26.0±7.1	53±26 (26-78)
400	1124±505	3.0 (2.0-4.0)	9458±2330	24.7±6.5	89±16 (72-116)
400 fasted	368±89.1	3.0 (2.0-4.0)	4194±1592	15.4±7.5	54±28 (27-99)

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

For C_{24h}, (min-max) is also shown.

IDX320 Phase I Study

Mean Plasma Concentrations of IDX320: 3-Day Dosing



IDX320 Phase I Study

Pharmacokinetic Parameters of IDX320: 3-Day Dosing

Dose (mg)	PK Day	C _{max} (ng/mL)	T _{max} (h)	AUC [#] (ng*h/mL)	T _{1/2} (h)	C _{24h} (ng/mL)
400	1	1154±381	3.0 (2.0-4.0)	10041±3855	12.2±1.8	117±53 (63-216)
	2					165±87 (87-333)
	3	1370±345	3.5 (3.0-6.0)	10026±4392	31.0±7.6	197±112 (119-420)

Values are reported as mean ± SD, except for T_{max} where medians (min-max) are reported. For C_{24h}, (min-max) is also shown. #AUC_{0-∞} for Day 1 and AUC_{0-24h} for Day 3 are reported.

IDX320 Phase I Study

Summary and Conclusions

- IDX320 was generally safe and well tolerated at oral doses up to 400 mg QD for 3 days in healthy male subjects.
- IDX320 was well absorbed with dose-related drug exposure.
- Food enhanced overall plasma exposure by approximately 2 fold.
- Mean IDX320 plasma C_{24h} concentrations after a single dose of 50-400 mg were dose proportional; ~3 to 30 fold above the GT 1a EC_{50} and ~20 to 200 fold above the GT 1b EC_{50} .
- After repeat daily dosing of 400 mg IDX320 for 3 days:
 - No appreciable accumulation with respect to peak/overall plasma exposure
 - IDX320 plasma C_{24h} concentrations on Day 3 were ~40 to 150 fold above the GT 1a EC_{50} and ~300 to 1000 fold above the GT 1b EC_{50}

IDX320 achieved plasma exposures above the targeted pharmacologically relevant drug exposure.

IDX320 Phase I Study

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