Population Pharmacokinetic (PopPK) Analysis of CRV431 in a Phase I Clinical Trial.

Mayo PR[1], Trepanier D[1], Ure D[1], and Foster RT.[1] *(1) Hepion Pharmaceuticals Inc.*

BACKGROUND

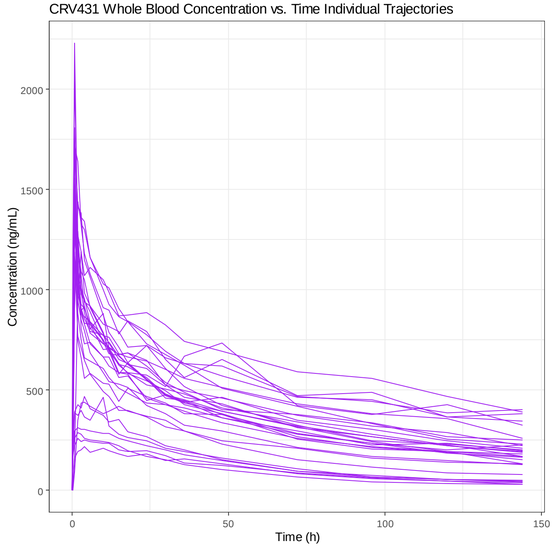
CRV431, a pan-cyclophilin inhibitor, has anti-viral activities in HBV, HCV, and HIV-1. It recently demonstrated efficacy in preventing fibrosis in precision cut human liver slices. The drug is currently being developed for use in non-alcoholic steatohepatitis (NASH). The objectives of this study were to establish safety and characterize the popPK of CRV431 to establish drug dosing for NASH patients.

METHODS

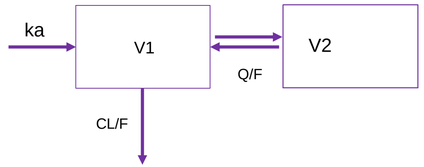
1. A phase I study assessed single ascending oral doses CRV431 from 75 mg to 525 mg combined with intensive pharmacokinetic sampling and safety evaluation.
2. Clinical laboratory and safety data were monitored for 21 days after receiving CRV431.
3. Data were analyzed using popPK non-linear mixed effects modeling (Nonmem7.4. with Pirana2.9.7), evaluating potential patient covariates that could contribute to pharmacokinetic variability.
4. A total of 36 covariates including patient demographics and clinical laboratory tests were evaluated.
5. Assay was LC/MS/MS BLQ 25 ng/mL

RESULTS

CRV431 Whole Blood Concentration vs. Time Individual Trajectories

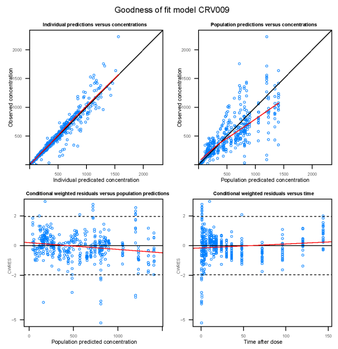


Model

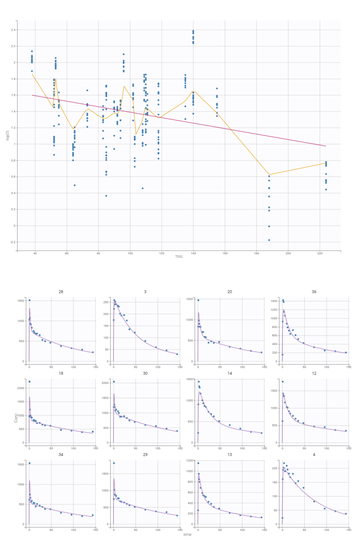


Parameter	Description	CRV001		CRV004		CRV011	
OFV	Objective function value	4833.749		4576.333		4357.822	
dOFV	OFV diff with CRV001	0		-257.416		-475.927	
TH 1	1 proportional error	0.265	5.50%	0.181	7.70%	0.174	7.40%
TH 2	2 additive error switched off	0*		0*		0*	
TH 3	3 KA h-1	3.71	12.50%	0.399	29.80%	0.567	27.3%
TH 4	4 CL/F L/H	4.3	7.60%	4.11	9.80%	3.93	6.4%
TH 5	5 CL/F ~ TRIG					-0.0814	20.6%
TH 6	6 V1/F L	344	7.10%	67.4	36.10%	88.2	27.8%
TH 7	7 Q/F L/h			57.5	22.30%	63.2	14.3%
TH 8	8 V2/F L			296	8.80%	269.0	8.0%
OM 1	1 [P] CL	0.114	22.70%	0.133	20.90%	0.0897	23.1%
OM 2	2 [P] V1	0.117	23.50%	0.403	16.50%	0.141	31.0%
OM 3	3 [P] Q			0.124	84.70%	0.168	19.0%
OM 4	4 [P] V2			0.183	17.90%	0.216	14.8%

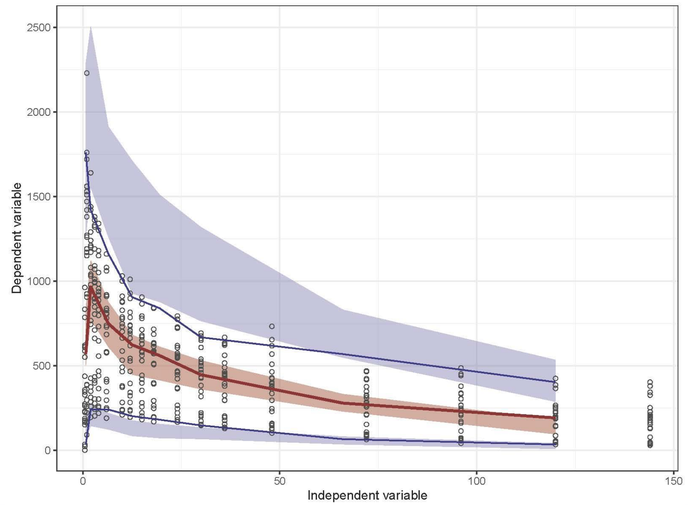
Goodness of Fit



$$CL/F = 3.93(TRIG/99)^{-0.0814}$$



Visual Predictive Check



CONCLUSIONS

- ✓ CRV431 can be administered as a fixed dose with no adjustment required for age, sex, body weight or ethnicity.
- ✓ As baseline serum triglycerides increase a modest reduction in oral clearance was observed.
- ✓ A negative correlation between serum triglycerides and cyclosporine A oral clearance has been previously reported.[1,2]
- ✓ This finding suggests that CRV431 was safe and well tolerated at all test doses after a single dose.

References

1. Wasan KM, Brocks DR, Lee SD, Sachs-Barrable K, Thornton SJ. Impact of lipoproteins on the biological activity and disposition of hydrophobic drugs: implications for drug discovery. Nature Reviews Drug Discovery. 2008 Jan;7(1):84.
2. Prueksaritanont T, Koike M, Hoener BA, Benet LZ. Transport and metabolism of cyclosporine in isolated rat hepatocytes: the effects of lipids. Biochemical pharmacology. 1992 May 8;43(9):1997-2006.

DISCLOSURES

Mayo, Trepanier, Ure and Foster are employees of Hepion Pharmaceuticals Inc.