A Phase 1 Single Ascending Dose Study of CRV431

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BACKGROUND

CRV431 is a non-immunosuppressive cyclosporine A (CsA) analog that displays a variety of therapeutic activities in experimental models as a result of its potent inhibition of cyclophilin isomerases. CRV431 anti-viral activities toward hepatitis B virus (HBV) and hepatitis C virus (HCV) are expected to reduce liver disease arising from viral hepatitis. Single dose rat and monkey studies demonstrated dose-dependent CRV431 exposures and half-lives ($t_{1/2}$) greater than 24 hours. These experiments along with other preclinical safety, ADME, and early toxicology results led to the development of a clinical program.

HBV: CRV431 decreases several HBV markers in cell culture and in an animal model, including HBV DNA, HBsAg, HBeAg, cccDNA, and pgRNA.[1]

HCV: CRV431 inhibits HCV replication by blocking cyclophilin A - NS5A binding.[2]

Fibrosis and Hepatocellular Carcinoma: CRV431 reduces fibrosis and tumor burden in mice with hepatocellular carcinoma.[3]

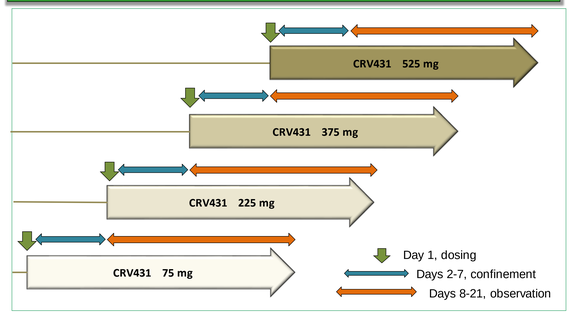
METHODS

The present, human single dose study was designed to investigate safety, tolerability, and pharmacokinetics (PK) of CRV431. CRV431 75, 225, 375 and 525 mg administered as a single oral dose to sequential dosing cohorts of healthy subjects randomized 3:1, active:placebo. Subjects were confined to the CRU for eight days -1 to 7 for PK sampling at times: pre-dose, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 10.0, 12.0, 15.0, 18.0, 24, 30, 36, 48, 72, 96, 120, 144 and 168 hours. One sentinel active and one placebo subject were dosed and observed for two days in each cohort before the remainder of cohort was dosed.

CTRV-CRV431-101:

- Part 1: Healthy subjects, sequential single ascending dose study (SAD), fasted conditions using a self-micro-emulsifying drug delivery system
- Part 2: Healthy subjects, CRV431-TDF drug-drug interaction study
- Part 3: 28 day safety and tolerability study in virally suppressed HBV+ patients

SAD Schematic



Disposition of Patients

Disposition	Pooled Placebo	75mg	225mg	375 mg	525 mg	375mg*	Total
Enrolled	10	6	6	6	6	6	30
Dosed	10	6	6	6	6	6	30
Completed	10	6	6	6	6	6	30
Discontinued Early	0	0	0	0	0	0	0

Baseline Characteristics

	Pooled Placebo	75 mg	225mg	375 mg	525 mg	375mg*	Total
N=40	10	6	6	6	6	6	30
Gender (n) Male:Female	3:7	3:3	3:3	2:4	1:5	3:3	12:18
Age [years]**	30.1 4.48	29.2 12.24	28.8 4.79	31.0 10.33	35.5 11.83	38.3 6.31	32.6 9.68
Race (n)							
Black	1	2	1	0	0	0	3
Other Race	0	1	0	0	0	0	1
White	9	3	5	6	6	6	26
BMI [kg/m]**	25.26 3.17	23.63 3.01	23.51 3.11	25.85 2.89	25.72 4.75	26.91 1.83	25.12 3.32

*ingested immediately following dilution
**mean, SD

Results

Summary of CRV431 Pharmacokinetics

Dose	T_{max} (range)	$C_{max, ng/mL}$ (SD)	AUC_{∞}, ng.h/mL (SD)	$t_{½}$, h (SD)
75mg	4 (2-10)	334±106	20,917±3,780	73.6±15.2
225mg	1.3 (1-2)	1,368±221	84,422±32,373	97.3±18.4
375mg	1.5 (1-3)	1,488±176	103,833±30,916	110.8±36.2
525mg	1.0 (1-1)	1,655±250	102,087±43,612	98.5±24.1

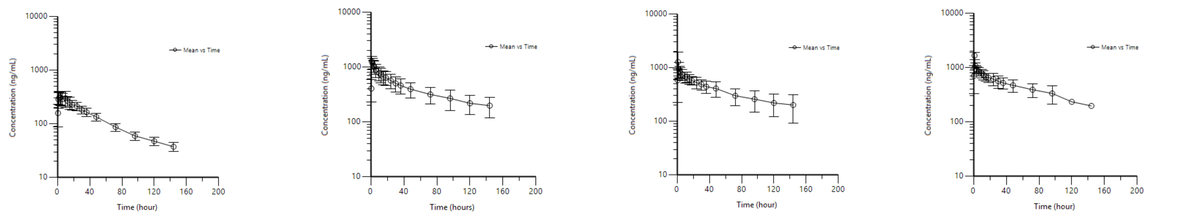
- Forty healthy subjects enrolled, 40 completed.
- Second cohort of 375mg was enrolled to optimize SMEDDS dosing.
- Dose exposure is linear up to 375mg.
- Baseline characteristics were comparable against treatment arms.

Number of Subjects with AEs by SOC

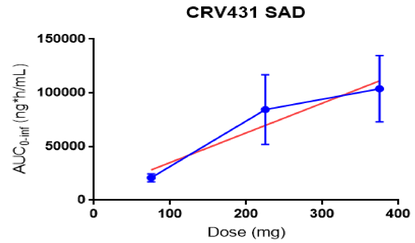
System Organ Classification	Pooled Placebo	75 mg	225mg	375 mg	525 mg	375mg*	Total
Number of Subjects Dosed	10	6	6	6	6	6	30
Number of Subjects with TEAEs	6	3	1	3	3	4	14
Number of Subjects without TEAs	4	3	5	3	3	2	16
Gastrointestinal Disorders	2	0	0	1	1	1	3
General Disorders and Administration Site Conditions	2	0	0	0	0	0	0
Infections and Infestations	0	1	0	0	0	1	2
Metabolism and Nutrition Disorders	1	1	0	0	0	0	1
Musculoskeletal Disorders	0	0	0	2	0	0	2
Nervous System Disorders	2	0	0	0	1	2	3
Skin Disorders	1	0	1	0	0	0	1
Respiratory, Thoracic and Mediastinal Disorder	1	1	0	0	1	0	2
Reproductive System and Breast Disorders	0	0	0	0	1	0	1

- There were no grade 3 or 4 AEs, SAEs or deaths.
- There were no patterns or dose-related trends in the nature, frequency or severity of AEs. The majority of events were mild.
- There were no clinically significant abnormalities, patterns or dose-related trends in PE findings, vital signs, ECGs or safety laboratory parameters.

75 mg | 225 mg | 375 mg | 525 mg



CRV431 Dose versus AUC



Goodness of Fit	
R square	0.914
Sy.x	18001

CONCLUSIONS

- **Single ascending doses were tested up to 525 mg with no concerns.**
- **The collective data from the SAD study demonstrate a favorable pharmacological, pharmacokinetic, and safety profile for CRV431.**
- **AEs reported were generally mild in nature and not related to study drug.**
- **These data along with the broad range of targeted anti-cyclophilin activity support further clinical development for chronic liver disease.**
- **Additional ongoing *in vitro* and *in vivo* studies support advancing CRV431 in NASH and HCC**

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