CRV431

HEPA-CRV431-201

AMBITION: A PHASE 2A, MULTI-CENTER, SINGLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF CRV431 DOSED ONCE DAILY IN NASH INDUCED F2 AND F3 SUBJECTS

Protocol Number	**HEPA-CRV431-201**
Study Drug	CRV431
Protocol Date/Version	February 27, 2020 / Version 1.0 March 23, 2020 / Version 2.0 May 06, 2020 / Version 3.0 July 14, 2020 / Version 4.0 March 01, 2021 / Version 5.0
Medical Monitor	[redacted]
Sponsor Contact	[redacted] Director, Clinical Operations Hepion Pharmaceuticals, Inc. 399 Thornall Street, First Floor Edison, NJ 08837 USA Phone: +1 (732) 902-4100
Sponsor	Hepion Pharmaceuticals, Inc. 399 Thornall Street First Floor Edison, NJ 08837 USA

NCT04480710

Confidentiality Statement

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for CRV431. I have read the attached protocol for study HEPA-CRV431-201 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

I will provide copies of the protocol and of the pre-clinical and clinical information on the Study Drug, which was furnished to me by the Sponsor, to all members of the study team responsible to me who participate in the study. I will discuss this material with them to assure that they are fully informed regarding the test article and the conduct of the study.

Once the protocol has been approved by the Investigational Review Board (IRB) or Independent Ethics Committee (IEC), I will not modify this protocol without obtaining the prior approval of the Sponsor and of the IRB/IEC. I will submit all protocol modifications and/or any informed consent modifications to the Sponsor and the IRB/IEC, and approval will be obtained before any modifications are implemented.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Clinical Study Lead	[redacted]	Hepion Pharmaceuticals, Inc. 399 Thornall Street First Floor Edison, NJ 08837 USA Phone: +1 (732) 902-4100
Responsible Physician 24-Hour Emergency Contact	[redacted]	[redacted]

2. SYNOPSIS

Name of Sponsor/Company: Hepion Pharmaceuticals, Inc.	
Name of Investigational Product: CRV431	
Name of Active Ingredient: Cyclo[L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-(3R,4R)-10-acetylamino-3-hydroxy-N,4-dimethyl-L-2-aminodecanoyl-L-2-aminobutanoyl-N-methyl-D-alanyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl]	
Title of Study: **A** Phase 2A, **M**ulti-center, Single-**B**l**i**nd, Placebo-controlled Study to Evaluate the Safety and **T**olerabil**i**ty of CRV431 Dosed **O**nce Daily in **N**ASH induced F2 and F3 Subjects	
Study Acronym: AMBITION	
Study center(s): approximately 10 U.S. sites	
Studied period (years): Estimated Q2 2020 to Q2 2021	**Phase of development:** 2A

Objectives:

Primary:

- To evaluate the safety and tolerability of once daily (QD) 75 mg and 225 mg doses of CRV431 in presumed nonalcoholic steatohepatitis (NASH) fibrosis stage 2 (F2)/fibrosis stage 3 (F3) subjects compared to placebo control over 28 days of dosing;
- To evaluate the pharmacokinetics (PK) of a QD dose of CRV431, its major metabolites and fraction unbound in presumed NASH F2/F3 subjects over 28 days of dosing.

Secondary:

- To evaluate non-invasively the antifibrotic activity of a QD dose of CRV431, as measured by quantification of selected biomarkers of fibrosis, in presumed NASH F2/F3 subjects over 28 days of dosing.

Exploratory Objectives:

- To generate exploratory data regarding the antifibrotic activity of a QD dose of CRV431 over 28 days of dosing by performing hepatic evaluations via laboratory assessments of biomarkers such:
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - Pharmacokinetic/pharmacodynamic (PK/PD) analyses to assess concentration effect relationship on all biomarkers;
  - Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) decrease from baseline.

Number of subjects (planned): Thirty-six (36) adult male or female subjects will be enrolled.

- **Cohort A:** Twelve (12) presumed NASH F2/F3 subjects on CRV431 75 mg QD;
- **Cohort B:** Six (6) presumed NASH F2/F3 subjects on matching placebo for Cohort A.
- **Cohort C:** Twelve (12) presumed NASH F2/F3 subjects on CRV431 225 mg QD;
- **Cohort D:** Six (6) presumed NASH F2/F3 subjects on matching placebo for Cohort C.

Methodology:

This is a randomized, single-blind, placebo-controlled, multi-center study to evaluate the safety and PK of CRV431 in subjects with presumed NASH F2/F3 fibrosis. Antifibrotic biomarker activity will be evaluated on an exploratory basis.

Cohort*	Fibrosis Stage	N	Day 1 – 28, fasted oral dosing	Day 29 - 42
A	F2/F3	12	CRV431 75 mg	Observation/Follow up
B		6	Placebo[a]	
C		12	CRV431 225 mg	
D		6	Placebo[b]	

*Randomized assignment; 2:1 – CRV431:Placebo
[a] Matching Placebo for Cohort A - 75 mg dose.
[b] Matching Placebo for Cohort C - 225 mg dose.

This study consists of 3 phases: (i) Screening and Randomization; (ii) treatment; and (iii) follow up. During Screening, each subject will provide informed consent prior to starting any study specific procedures. The randomization of subjects in each cohort will be performed in a 2:1 ratio (12 CRV431 subjects and 6 placebo subjects). During the treatment period, randomized subjects will be provided the treatment and assessments according to Schedule of Events, Table 3. In the follow up phase, investigational product (IP) will be discontinued followed by 14 Days of safety follow-up. Subjects randomized into either Cohort A or Cohort B will receive a 75 mg QD dose of CRV431 or matching placebo in a fasted state, respectively. Subjects randomized into either Cohort C or Cohort D will receive a 225 mg QD dose of CRV431 or matching placebo in a fasted state, respectively.

Safety and available PK data will be reviewed by a DSMB prior to proceeding with the next higher dose cohort. The DSMB will also conduct a safety review if stopping criteria are met.

Subjects who do not complete the study may be replaced within the dosing cohort, unless a stopping rule (see Section 7.5) precludes replacement.

Subjects who miss more than 2 consecutive QD doses of CRV431 may be replaced, unless a stopping rule (Section 7.5) precludes replacement.

Inclusion and Exclusion Criteria:

Inclusion Criteria

Subjects must fulfill all the following inclusion criteria to be eligible for participation in the study.

1. Capable of giving written informed consent and able to effectively communicate with the investigator and study personnel. A signed informed consent form (ICF) must be on file prior to initiating the Screening procedures;
2. Willing and able to complete all study requirements, restrictions, visits and procedures;
3. AST ≥ 20 IU/L and FibroScan ≥ 8.5 kPa values. Historical value of FibroScan obtained within 3 months prior to Screening can be accepted. If historical value is not available, a FibroScan must be obtained as part of Screening. If a potential subject does not meet the inclusion AST and/or FibroScan requirements, a historical biopsy obtained within 6 months confirming NASH F2 fibrosis stage or a historical biopsy obtained within 12 months confirming NASH F3 fibrosis stage can be accepted to supersede the AST and/or FibroScan results;
4. [redacted]
5. Male or female between 18 and 75 years of age (inclusive);
6. Females of reproductive potential, defined as women who have not been postmenopausal for at least 24 consecutive months (i.e., who have had menses within the preceding 24 months), or women who have not undergone surgical sterilization, specifically, hysterectomy, bilateral salpingectomy, bilateral oophorectomy, hysteroscopic sterilization, and/or tubal ligation, must have a negative pregnancy test at Screening and within the 24-hour period prior to Day 1;
7. All participants must agree not to participate in a conception process (i.e., active attempt to become pregnant or to impregnate, sperm or egg donation, in vitro fertilization). If participating in sexual activity that could lead to pregnancy, the participant must agree to use 2 reliable methods of contraception simultaneously while receiving study treatment and for 3 months after subject has stopped taking study drug. A combination of TWO of the following methods MUST be used appropriately:
   a. Condoms (male or female) with or without a spermicidal agent;
   b. Diaphragm or cervical cap with spermicide;
   c. Intrauterine device (IUD);
   d. Hormonal-based contraception.

   Note: Participants who are not of reproductive potential (women who have been postmenopausal for at least 24 consecutive months or have undergone hysterectomy, bilateral salpingectomy, bilateral oophorectomy, hysteroscopic sterilization, and/or tubal ligation, or men who have documented azoospermia) are eligible without requiring the use of contraceptives. Acceptable documentation of sterilization, menopause or male partner's azoospermia must be provided; serum follicle stimulating hormone (FSH) measurement can be used to document menopausal status.

Exclusion Criteria

Subjects who meet any of the following criteria prior to the first dose of study drug are not eligible for randomization.

1. Pregnant or breastfeeding or planning to become pregnant during the study period;
2. Known allergy to CRV431, cyclosporine, or any of their inactive ingredients;
3. Positive test for hepatitis B surface antigen (HBsAg), hepatitis C virus antibodies (HCVAb) or human immunodeficiency virus antibodies (HIVAb). If HCVAb test is positive, then an HCV-RNA test will be performed. If the HCV-RNA test is negative, the subject is allowed to participate in the study, as long as the subject meets all other inclusion criteria and has never been treated for HCV or was treated >2years ago and achieved a sustained virologic response at that time;
4. History of or any current medical condition which could compromise the safety of the participant in the study, as determined by the investigator;
5. Subjects with a systolic pressure >150 or a diastolic pressure >90. At the discretion of the investigator, the blood pressure may be re-measured after 10 minutes to ensure the blood pressure is in fact out of range. Out of range blood pressure after the second measurement will exclude a subject. If a subject has a blood pressure within the desired range due to anti-hypertension medication, that subject can be included at the discretion of the investigator, provided the anti-hypertension medication is not a contraindicated medication. Please refer to Appendix A for a list of drugs considered contraindicated;
6. Clinically significant gastrointestinal, cardiovascular, neurologic, psychiatric, metabolic, renal, hepatic, respiratory, inflammatory, or infectious disease, as determined by the investigator;
7. Subjects with a history of clinically significant acute cardiac events within 6 months prior to Screening such as stroke, transient ischemic attack, or coronary heart disease (angina pectoris requiring therapy, myocardial infarction, revascularization procedures with left ventricular ejection fraction [LVEF] <50% as determined by previous echocardiography or multiple gated acquisition [MUGA] scan);
8. Subjects with uncontrolled or unstable cardiac arrhythmias:
    a. Severe conduction disturbance (e.g., second-degree or third-degree AV block);
    b. QTc-interval >450 msec (males) or >470 msec (females);
    c. History of congenital long QT syndrome, congenital short QT syndrome, Torsades de Pointes, or Wolff Parkinson White syndrome;
9. Subjects with transaminases >5 x upper limit of normal (ULN) and with alkaline phosphatase (ALP) >2 x ULN;
10. Subjects with total serum bilirubin >1.5 x ULN, unless the subject has Gilbert's Syndrome, in which case the subject can be enrolled provided the direct bilirubin is within 30% of the total bilirubin (TBL);
11. Subjects with a platelet count <150,000/m^3;

12. Systemic immunosuppression within 6 months prior to the first dose of study drug apart from short-term treatment for asthma, COPD or other respiratory conditions;
13. Current clinically significant diarrhea or gastric stasis that, in the investigator's opinion, could influence drug absorption or bioavailability;
14. Subject with any history or presence of decompensated cirrhosis;
15. Other well documented causes of chronic liver disease according to standard diagnostic procedures including, but not restricted to:
    a. Suspicion of drug-induced liver disease;
    b. Alcoholic liver disease;
    c. Autoimmune hepatitis;
    d. Wilson's disease;
    e. Primary biliary cholangitis, primary sclerosing cholangitis;
    f. Genetic hemochromatosis (Homozygosity for C282Y or C282Y/H63D compound heterozygote);
    g. Known or suspected hepatocellular carcinoma (HCC);
    h. History or planned liver transplant, or current Model for End-Stage Liver Disease (MELD) score >15;
16. History of, or current evidence of, gallstones, gall bladder disease, cholestasis that has not been treated with cholecystectomy, or pancreatitis;
17. Subjects with hemoglobin A1c (HbA1c) >9.5%. For subjects with an HbA1c >9.5% at the Screening Visit, a repeat test may be performed. A repeat HbA1c result >9.5% will lead to exclusion;
18. At Screening, an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (calculated by the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] method) and/or a Kidney Disease Improving Global Outcomes (KDIGO) category of >G2;
19. Safety laboratory abnormalities at Screening which are clinically significant as determined by the investigator;
20. Weight loss of more than 5% within 3 months prior to randomization;
21. Current abuse of alcohol or illicit drugs, or history of alcohol or illicit drug abuse within the preceding 2 years, as determined by the investigator. History of excess alcohol intake as defined by ≥21 units of alcohol per week in males and ≥14 units of alcohol per week in females for 2 years prior to enrollment where a "unit" of alcohol is equivalent to 12-ounce beer, 4-ounce of wine, or 1-ounce shot of hard liquor;
22. A positive urine drug screen for drugs with a high potential for abuse (amphetamines, cannabinoids, opiates, cocaine, benzodiazepine) or alcohol test at Screening or Day -1. For benzodiazepine's only: positive results will be accepted if due to an approved prescription. For cannabinoids, opiates and amphetamines: On a case by case basis, positive results will be evaluated by the Sponsor and Medical Monitor in order to determine the subject's eligibility to safely be included in the study;
23. Significant medical or psychiatric illness that would interfere with compliance and ability to tolerate treatment as outlined in the protocol;

24. Subjects who cannot be contacted in case of emergency;
25. Judgement by the investigator that the subject should not participate in the study if the subject is unlikely to comply with all study procedures and treatment;
26. Received an investigational drug or investigational vaccine or used an investigational medical device within 30 days prior to first dose of study drug;
27. Subjects who have used any drugs or substances known to be strong inhibitors or inducers of cytochrome P4503A4/5 (CYP3A4/5) and drugs whose major elimination pathway is the bile salt export pump (BSEP) or organic anion transporter 3 (OAT3), and drugs that are major substrates of the hepatic uptake transporters, organic anion transporting polypeptide1B1 (OATP1B1) and OATP1B3 within 30 days prior to the first dose of study drug. (**NOTE**: Please refer to Appendix A for a list of drugs considered contraindicated. If there are questions, please contact the sponsor);
28. Subjects with a history of organ transplantation. Corneal transplantation will be allowed.

Abnormal electrocardiogram (ECG) or laboratory parameters may be repeated once, if in the opinion of the investigator, the results are due to technical factors or are inconsistent with the potential subject's medical evaluation.

Potential study subjects who met all inclusion and none of the exclusion criteria for this study but who, for personal or administrative reasons, were not included in a study cohort may be re-screened if more than 30 days have passed since their previous Screening. For these subjects, use of ELF or Pro-C3 results previously obtained for this study will be extended for an additional 30 days up to a total of 60 days. There are no restrictions on the number of re-screens permitted for these subjects.

[redacted]

Investigational product, dosage and mode of administration:

- CRV431, 75 mg, softgel capsule, orally QD, in fasted condition
- Placebo, softgel capsule orally QD, in fasted condition

Duration of treatment: Full treatment duration will be defined as 28 days of treatment with CRV431 or placebo.

Criteria for evaluation:

Safety:

Safety and tolerability parameters, including adverse events (AEs), serious adverse events (SAEs), AEs of special interest, physical examinations including weight and height, concomitant medications, laboratory assessments including blood chemistry, hematology and coagulation, urinalysis, pregnancy screening, clinical safety laboratory parameters, ECG, and vital sign assessments, will be determined.

Pharmacokinetics:

Whole blood PK samples will be analyzed for the concentrations of CRV431 along with its major metabolites using a validated liquid chromatography/tandem mass spectroscopy (LC-MS/MS) assay. Subjects will have whole blood PK samples collected at the following time points on Days 1 and 28: 0 hour (pre-dose), 2.0, 4.0 and 8.0 hours (post-dose). A single sample of whole blood will be collected for PK on Day 14 (pre-dose). Standard non-compartmental PK parameters will be calculated from whole blood.

Statistical methods:

The sample size is not based on statistical considerations. It is expected that the number of subjects per cohort, 12 subjects in Cohort A, 6 subjects in Cohort B, 12 subjects in Cohort C and 6 subjects in Cohort D is enough to assess the safety, tolerability, and PK of CRV431, as well as providing a preliminary indication of its antifibrotic activity, based on biomarkers, for Phase 2B study planning purposes. To evaluate drug effect and dose response, comparisons of Cohorts will include Cohort A versus Cohort B, Cohort C versus Cohort D and Cohort A versus Cohort C.

Data will be listed by subject and summarized using descriptive statistics. [redacted]

3. TABLE OF CONTENTS AND LIST OF TABLES

TABLE OF CONTENTS

LIST OF TABLES

4. LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviations/Acronyms	Definition
AE(s)	Adverse event(s)
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration time curve
AUC_{0-24}	Area under the concentration time curve from time 0 to the 24-hour time point
AUC_{0-48}	Area under the concentration time curve from time 0 to the 48-hour time point
AUC_{0-last}	Area under the concentration time curve calculated from 0 to the last observed concentration
AUC_{0-inf}	Area under the concentration time curve from 0 to infinity
AUC_{0-t}	Area under the concentration time curve from time zero to time t
$\%AUCt_{expol}$	Percentage of AUC_{0-inf} extrapolated beyond T_{last}
CL/F	Apparent total oral clearance (parent compound only)
C_{max}	Maximum observed whole blood concentration
C_{min}	Minimum observed whole blood concentration
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
IEC	Independent Ethics Committee
IRB	Institutional Review Board
NAFLD	Nonalcoholic fatty liver disease
f_u	Fraction Unbound
PK	Pharmacokinetics
PK/PD	Pharmacokinetics/Pharmacodynamics
QD	Once daily
QTcF	Friderica's QT Correction Formula
SAE(s)	Serious adverse event(s)
V_z/F	Apparent volume of distribution during the terminal elimination phase

5. INTRODUCTION

5.1. Background

Nonalcoholic fatty liver disease (NAFLD) and its more severe form, nonalcoholic steatohepatitis (NASH) are significant health burdens and are on the rise across the globe. Nonalcoholic fatty liver disease is characterized by fat accumulation in the liver and often is associated with obesity, insulin resistance, diabetes mellitus, dyslipidemia, hypertension, and other aspects of metabolic syndrome. Nonalcoholic steatohepatitis shares these characteristics but additionally is characterized by liver inflammation, hepatocyte necrosis and potentially fibrosis, which places patients at increased risk of developing cirrhosis and liver cancer.

The prevalence of NAFLD, NASH and HCC are on the rise throughout the world. In a recent study published by Estes et al. (Estes, 2018), NAFLD cases in the USA are projected to increase from 83.1 million in 2015 to 100.9 million in 2030. This equates to a 33.5% prevalence among adults over the age of 15. Nonalcoholic steatohepatitis cases in the USA are projected to rise from 16.5 million in 2015 to 27 million in 2030. In addition, the incidence of HCC is projected to increase by 137% from 2015 to 2030 leading to an increase in liver related deaths. From 2015 to 2030, the estimate of nearly 800,000 excess liver deaths are expected. From a global perspective, NAFLD prevalence is 25.4% with the highest rates in the Middle East and South America. This correlates with a 40.76% rate of NASH and/or fibrosis progression. The HCC incidence was 0.44 per 1,000 person years in NAFLD patients. Liver associated mortality had a higher risk ratio 1.94 compared to overall mortality 1.05 in a NAFLD patient population (Siddiqui, 2018). When looking at the USA, it is reported the NAFLD rates to be between 10 and 30%. These rates also apply to Europe and Asia (Younossi, 2016).

There are currently no USA Food and Drug Administration (FDA) approved medications specifically for NAFLD or NASH, but many drug candidates are in development.

Many pathological processes contribute to NASH, including the toxic effects of fat accumulation, oxidative stress, cell injury and cell death, leukocyte recruitment and activation of infiltrating cells and resident macrophages, profibrogenic activation of hepatic stellate cells, fibrosis, and carcinogenic transformation of liver cells. Effective therapies for NASH likely will require targeting multiple pathogenic mechanisms. Targeting late-disease processes, especially those related to fibrosis, is especially important. Most patients with NAFLD and early NASH are asymptomatic and therefore it is expected that they will already have moderately advanced NASH by the time that they are diagnosed. Also, fibrosis is the strongest predictor of adverse clinical outcomes associated with NASH such as progression to cirrhosis and HCC. Whereas therapies targeting dyslipidemia, inflammation, and other triggers of NASH will be important for halting disease progression, it is vitally important to develop treatments that more directly inhibit fibrogenesis, stimulate fibrolysis, promote restoration of liver function, reduce the risks of carcinogenesis, and restrict tumor progression. CRV431 is a drug candidate that is proposed to directly target many of these pathological events.

5.2. Rationale

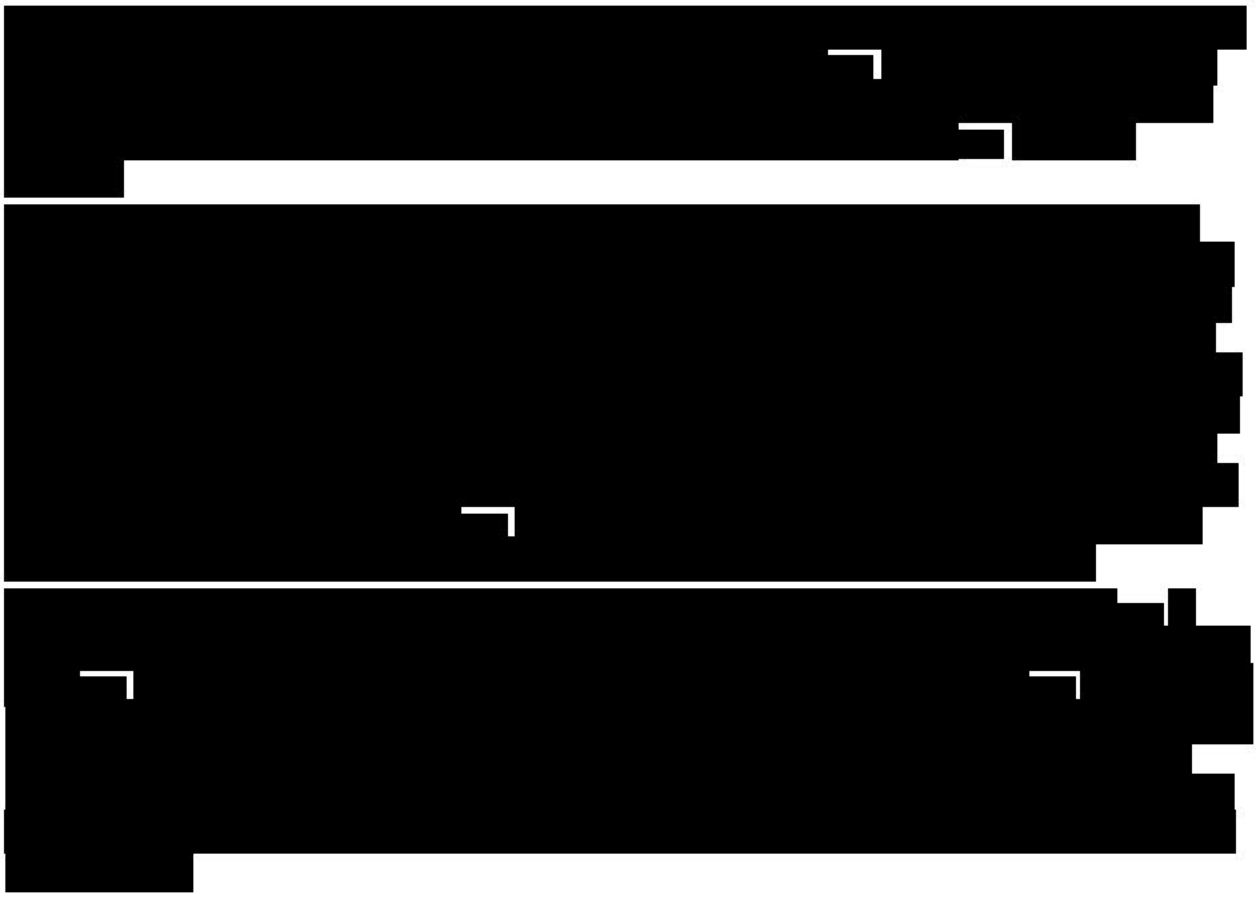
CRV431 is a chemically modified analog of the immunosuppressive drug, cyclosporine A (CsA). Cyclosporine A exerts its immunosuppression by a two-step process. Cyclosporine A first binds

to cyclophilin A (Cyp A), a peptidylprolyl isomerase that regulates target protein structure and function by influencing the cis-trans conformation of proline peptide bonds. Then the CsA-Cyp A duplex binds to and inhibits the activity of the phosphatase, calcineurin, in lymphocytes. CRV431 is chemically and functionally different from CsA in that it retains binding to Cyp A, but the CRV431-cyclophilin duplex does not strongly bind to calcineurin and therefore does not have significant immunosuppressive potential.

CRV431 binding and inhibition of Cyp A is 13-times more potent than that of CsA with an inhibitor constant, Ki = 1 nM, and it is this high-affinity, cyclophilin inhibition that is proposed to mediate therapeutic effects of CRV431. Moreover, CRV431 inhibits not only Cyp A but also other cyclophilin isoforms, notably cyclophilin B (Cyp B) and cyclophilin D (Cyp D), which contribute to a variety of pathological processes (Nigro et al., 2013; Naoumov, 2014; Bukrinsky, 2015; Dawar et al., 2017a, b; Briston et al., 2018; Wang et al., 2018; Xue et al., 2018). For example, Cyp A is an abundant cytosolic cyclophilin that influences many intracellular signaling pathways. It is released from injured cells and stimulates inflammation by binding to CD147 and contributes to cancer cell adaptation to hypoxia and is recruited into the life cycles of many viruses, including hepatitis B virus (HBV) and hepatitis C virus (HCV). Cyclophilin B is located in the endoplasmic reticulum where it participates in protein folding and secretion of proteins. Notably, Cyp B regulates procollagen hydroxylation, formation of procollagen triple-helices, and rates of secretion of procollagen from cells. Impairment of Cyp B-regulated procollagen production is hypothesized to be the major mechanism by which CRV431 decreases liver fibrosis. Cyp D is located in the mitochondrial matrix and is the primary regulator of mitochondrial permeability transition pores (mPTP). These mitochondrial pores open in response to common types of cellular injury, such as oxidative stress and calcium overload, leading to mitochondrial destruction and cell necrosis. Inhibition of Cyp D protects cells from a variety of insults and may be important for reducing cell loss and ensuing pathological cascades in NASH livers. Cyclophilin D also is implicated in liver steatosis and in oncogenic events related to the tumor suppressor, p53, to which Cyp D binds. In summary, several cyclophilin-dependent pathological processes in NASH livers are likely to be attenuated by CRV431. For information on mechanism of action and additional preclinical data, please refer to the CRV431 Investigational Brochure.

5.3. Rationale for this Study Design and Dose Selection

CRV431 has consistently demonstrated the ability to prevent the progression of liver fibrosis in a variety of animal models and in precision-cut human liver slices. The primary mechanism of action to prevent collagen synthesis is via Cyp B inhibition although additional mechanisms may involve Cyp A and Cyp D. The half maximal inhibitory concentration (IC50) for cyclophilin inhibition ranges from 3.2 to 9.5 ng/mL. Human whole blood concentrations after a single dose 75 mg of CRV431 achieved a maximum observed whole blood concentration (C_{max}) of 334 ± 106 ng/mL. Steady state concentrations for 75 mg QD dosed for 28 days achieved a C_{max} of 1397.5 ± 97.8 ng/mL with a mean trough level of 889.5 ± 70.4 ng/mL demonstrating that whole blood concentrations are above the cellular IC50 range for the entire dosing period which ensures target engagement. In order to evaluate the potential dose response of CRV431 on safety and NASH biomarkers, a second dose of 225 mg QD demonstrating a steady-state Cmax of 1844 ± 321.9 ng/mL will be explored.

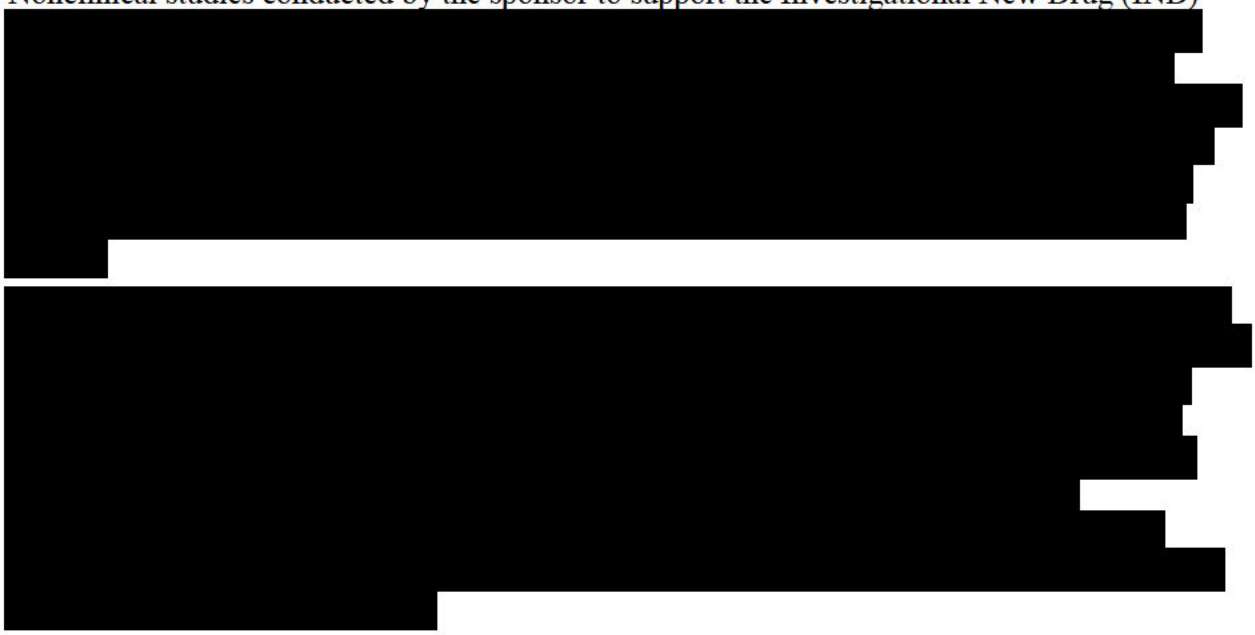


The use of AST and Pro-C3 have been increasingly used to identify fibrosis progression in NASH subjects. Aspartate aminotransferase has been used to stratify patients as a sole indicator or as an integral part of NASH scoring systems. Type III collagen neo-epitopes (Pro-C3) has emerged as a biomarker indicative of active fibrogenesis. Given that the primary pharmacological mechanism of CRV431 is to directly influence the rate of fibrogenesis, Pro-C3 and AST are known biological indicators of active fibrogenesis. The use of these biomarkers in the inclusion criteria for subject selection ensures subjects have active disease with fibrogenesis. Both markers provide a more adequate assessment of disease activity than serial measurements of liver transaminases alone. Given the duration of the study and the sample size of this Phase 2a trial, it is essential to enrich the study design by including patients with active fibrogenesis. While serial transaminases measurements, repeated 3 to 4 weeks apart can indicate disease progression, transaminases lack the specificity provided by AST and Pro-C3. Thus, an inclusion criterion of AST >20 IU/L combined with a Pro-C3 >15.5 ng/mL precludes the need for multiple pre-Screening liver enzyme testing (Schuppan D, et al., 2018).

5.4. Risks and/or Benefits to Subjects

This is the first study of CRV431 in subjects with presumed NASH F2/F3 fibrosis. As this is a Phase 2a trial designed to evaluate safety, PK and biomarkers of fibrosis, subjects who participate in this study are not expected to derive any clinical benefit over the course of the 28-day study. Subsequently, liver biopsies for entry are not required.

Currently, there is no standard of care for NASH patients although life-style intervention including weight loss and alterations in diet are routinely recommended with bariatric surgery for overweight patients (see American Association for the Study of Disease Guidelines for NAFLD). Nonclinical studies conducted by the sponsor to support the Investigational New Drug (IND)



6. STUDY OBJECTIVES

6.1. Primary Objectives

- To evaluate the safety and tolerability of QD 75 mg and 225 mg doses of CRV431 in presumed NASH F2/F3 subjects compared to placebo control over 28 days of dosing;
- To evaluate the PK of a QD dose of CRV431, its major metabolites and fraction unbound in presumed NASH F2/F3 subjects over 28 days of dosing.

6.2. Secondary Objective

- To evaluate non-invasively the antifibrotic activity of a QD dose of CRV431, as measured by quantification of selected biomarkers of fibrosis, in presumed NASH F2/F3 subjects over 28 days of dosing.

6.3. Exploratory Objectives

- To generate exploratory data regarding the antifibrotic activity of a QD dose of CRV431 over 28 days of dosing by performing hepatic evaluations via laboratory assessments of biomarkers [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - ALT and/or AST decrease from baseline.

6.4. Study Endpoints

6.4.1. Safety Endpoints

Safety and tolerability parameters, including AEs, SAEs, AEs of special interest, physical examinations including weight and height, concomitant medications, laboratory assessments including blood chemistry, hematology and coagulation, urinalysis, pregnancy screening, ECG, and vital sign assessments, will be determined.

6.4.2. Pharmacokinetic Endpoints

The PK parameters for CRV431 in whole blood will be determined in subjects in fasted state. A list of PK parameters is shown in Table 5.

On an exploratory basis, concentration-effect relationships will be explored between CRV431 whole blood concentrations and all biomarkers measured. Subject demographics and clinical laboratory data will be evaluated as potential covariates in PK/PD model using non-linear mixed effect modeling with direct and indirect models.

[redacted]

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a randomized, single-blind, placebo-controlled, QD dose study of CRV431 in presumed NASH F2/F3 subjects. This study will consist of 3 phases: (i) Screening and Randomization; (ii) treatment; and (iii) follow up.

7.1.1. Screening and Randomization Period

Screening visits will be conducted within 30 days prior to study Day 1. During the Screening Phase, each potential subject will provide informed consent prior to starting any study-specific procedures.

Due to the logistics and time needed for the retest of the [redacted], for those subjects that an investigator requests a retest of these samples, as described in Section 8.2, the screening period may be extended an additional 30 days for a screening period of up to 60 days total in order to allow subjects who are waiting the retest results the opportunity to meet all study entry criteria.

Once a subject is considered eligible, prior to Day 1, a concomitant medication form will be completed by the site and sent to the sponsor for approval. See Section 7.4.1 for prohibited medications.

Subjects who are eligible will be randomized as described in Section 7.3.3 and as shown in Table 2.

Table 2: Study Design

Cohort*	Fibrosis Stage	N	Day 1 – 28, fasted oral dosing	Day 29 - 42
A	F2/F3	12	CRV431 75 mg	Observation/Follow up
B		6	Placebo[a]	
C		12	CRV431 225 mg	
D		6	Placebo[b]	

*Randomized assignment; 2:1 – CRV431:Placebo
[a] Matching Placebo for Cohort A - 75 mg dose.
[b] Matching Placebo for Cohort C - 225 mg dose.

Potential study subjects who meet all inclusion and exclusion criteria for this study, but who, for personal or administrative reasons, are not included in the study may be re-screened if more than 30 days has passed since their previous screening. For these subjects, use of [redacted] results previously obtained for this study will be extended for an additional 30 days up to a total of 60 days. There are no restrictions on the number of re-screens permitted.

Potential study subjects who previously screened and failed only [redacted] but met all other inclusion criteria and met none of the exclusion criteria for this study may be re-screened.

7.1.2. Treatment Period

Subjects will receive treatment with CRV431 or matching placebo from Day 1 to Day 28. Study visit days that include treatment administration occur on Days 1, 2, 7, 14, and 28. Visit windows will be allowed and are as follows: Day 7 and Day 14, the visit window is ± 1 day and Day 28 the visit window is + 2 days. If the study visit for Day 28 is extended, the subject must continue taking study drug until the visit is completed.

Whole blood samples will be collected pre-dose and through Day 42 or early termination for safety and PK assessments as shown in Table 3 and Table 6, respectively. AEs will be collected as described in Section 11.4.

7.1.3. Follow Up Period

After completion of the treatment period, the subjects will be monitored for additional 14 days. A visit window of ±2 days will be allowed for the Day42/EOS visit.

Subjects who do not complete the study may be replaced within a dosing cohort, unless a stopping rule precludes replacement. Safety criteria for dose adjustments or stopping rules are provided in Section 7.5.

The overall study design of all scheduled procedures is shown in Table 3.

Table 3: Schedule of Events

Procedure	Screening (Day -30 to -2)	Day -1	Day 1	Day 2	Day 7 (±1)	Day 14 (±1)	Day 28 (+2)	EOS/ Day 42 (±2)	ET[a]
Informed Consent[b]	X								
Demographics	X								
Weight and height	X								
HIV, HBV, HCV tests	X								
Physical exam	X								
Medical history	X								
Inclusion/exclusion	X	X							
Randomization		X							
Pregnancy test[c]	X	X						X	X
FSH	X								
Drugs of abuse and alcohol screen	X	X							X
Vital signs[d]	X	X	X	X	X	X	X	X	X
ECG[e]	X	X	X	X	X	X	X	X	X
Blood chemistry[f]	X	X	X	X	X	X	X	X	X
Hematology and Coagulation	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X
PK[g]			X			X	X		X[h]
Fraction Unbound[g]			X				X		
ELF Score	X						X		

Procedure	Screening (Day -30 to -2)	Day -1	Day 1	Day 2	Day 7 (±1)	Day 14 (±1)	Day 28 (+2)	EOS/ Day 42 (±2)	ET[a]
[redacted]	X[i]		X			X	X	X	X
[redacted]			X			X	X	X	
[redacted]			X			X	X	X	
[redacted]			X				X		
[redacted]	[redacted]						[redacted]		
Study Drug Administration[k]			←	—	—	—	→		
Adverse events	←	—	—	—	—	—	—	→	X
Concomitant medications	←	—	—	—	—	—	—	→	X

Abbreviations: ECG, electrocardiogram; EOS, End of Study; ET, Early Termination; FSH, follicle stimulating hormone; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PK, pharmacokinetic(s).

[a] If an Early Termination visit and a scheduled visit coincide, procedures for both visits should be completed without duplication.

[b] Subjects must provide written informed consent prior to initiating any study procedures. To participate in this study, subjects must consent to all procedures outlined in Table 3, [redacted]

[c] All females of childbearing potential will have a serum beta human chorionic gonadotropin pregnancy test or urine dipstick pregnancy test at Screening, and urine dipstick pregnancy tests at all other indicated visits.

[d] Blood pressure will be measured with a standard mercury sphygmomanometer or an automated oscillometric blood pressure monitor after the subject has been resting in a supine position for at least 5 minutes. Heart rate will be measured by an automated vital signs machine. Respiratory rate will be measured only if medically indicated.

[e] Twelve-lead ECGs should be performed after the subject has been supine for 5 minutes and should be scheduled 1½ to 3 hours after the morning dose. On Day 1 and Day 28, ECGs will be performed prior to the 2 hr. PK draw. ECGs performed on non-dosing Days should be completed within the same time window as the ECGs that were done 1½ to 3 hours after the time the morning doses were administered. The timing of the ECG may be adjusted to C_{max} as new data becomes available.

[f] HbA1c will be checked at Screening, D28, EOS and ET only.

[g] Subjects in all cohorts will have blood PK and fraction unbound samples collected at the time points indicated in Table 6.

[h] PK not performed if ET visit occurs after Day 28.

[i] At Screening, only Pro-C3 will be analyzed. At all other time points all collagen biomarker listed in Section 6.3 will be analyzed.

[j] Obtained within 3 months prior to Screening or during Screening Period.

[k] On Day 1 and Day 28, subjects will fast overnight for at least 8 hours, will take CRV431 or matching placebo and will fast for an additional 2 hours following receipt of study drug. On subsequent days subject will fast overnight for at least 8 hours, will take CRV431 or matching placebo and will fast for an additional 30 minutes following receipt of study drug.

7.2. Number of Subjects

A total of 36 adult male or female subjects with presumed NASH F2/F3 will be enrolled. Of the 36 subjects, 12 subjects will be enrolled in Cohort A to receive 75mg of CRV431, 6 subjects will be enrolled in Cohort B to receive the matching placebo of Cohort A, 12 subjects will be enrolled in Cohort C to receive 225mg of CRV431 and 6 subjects will be enrolled in Cohort D to receive the matching placebo of Cohort C.

7.3. Treatment

Subjects in Cohort A will receive CRV431 75 mg (1 x 75 mg softgel capsule) QD and subjects in Cohort B will receive the matching placebo (1 x placebo softgel capsule) for Cohort A.

Subjects in Cohort C will receive CRV431 225 mg (3 x 75 mg softgel capsules) QD and subjects in Cohort D will receive the matching placebo (3 x placebo softgel capsules) for Cohort C.

7.3.1. Treatment Administration

Subjects will take study drug on the morning of each dosing day, with approximately 240 mL of water. On Day 1 and Day 28, subjects will fast overnight for at least 8 hours, will take CRV431 or matching placebo and will fast for an additional 2 hours after treatment administration. On subsequent days, subject will fast overnight for at least 8 hours, will take CRV431 or matching placebo and will fast for an additional 30 minutes after treatment administration. On visit days, the exact time of dosing will be decided based on logistics and will be documented in the source documents.

7.3.2. Treatment Compliance

While in the Clinical Research Unit, study treatment will be administered under the supervision of site personnel. Compliance during the non-study visit days will be assessed by subject reporting and pill count. Study personnel should counsel subjects on study medication compliance during each study visit. A qualified designee will be responsible for monitoring the administration of the timed oral doses on study visit days.

7.3.3. Randomization and Blinding

Upon determination that a subject meets all eligibility criteria, the subject will be randomized on Study Day -1 to receive either CRV431 or matching placebo in a 2:1 subject ratio (12 CRV431 75mg to 6 matching placebo and 12 CRV431 225mg to 6 matching placebo) in accordance with a computer-generated randomization schedule generated by a non-study statistician. Using this randomization schedule, pharmacy staff or designee will assign treatment sequentially to each eligible subject within a given cohort.

This is a single blind study where the investigator and sponsor are unblinded. However, the subject is blinded and will not know if he or she will receive CRV431 or matching placebo.

7.4. Study Restriction

7.4.1. Prohibited and Concomitant Medication

Any prescription medication or over the counter medication taken from 30 days prior to the time of consent to the End of Study/Early Termination Visit will be recorded in the subject's medical record (source document) and Case Report Form (CRF).

Once a subject is considered eligible, prior to Day 1, a concomitant medication form will be completed by the site and reviewed by the sponsor for approval.

Use of the following medication prior to and during the study is prohibited:

- Any drugs or substances known to be strong inhibitors or inducers of CYP3A4/5 and drugs whose major elimination pathway is via the BSEP or OAT3 transporters, and drugs that are major substrates of the hepatic uptake transporters OATP1B1 and OATP1B3 received within 30 days prior to the first dose of study drug. (**NOTE**: Please refer to Appendix A and if there are questions, please contact the sponsor);
- Systemic immunosuppressants, with the exception of short-term treatment for asthma, received within 6 months prior to the first dose of study drug and during the study;
- Any investigational product or investigational device received within 30 days prior to the first dose of study drug and during the study.

For questions regarding the use of medications, the investigator should contact the sponsor for further discussion. In case of an acute medical emergency, discussion with the Sponsor is excluded and the subject should be treated according to the judgement of the PI.

Consumption of foods and beverages containing the following substances will be prohibited as indicated:

- Xanthines/caffeine: 24 hours prior to dosing and throughout the period of PK sample collection;
- Alcohol: 48 hours prior to dosing and throughout the period of PK sample collection;
- Grapefruit/Seville orange: 14 days prior to dosing and throughout the period of PK sample collection.

7.4.2. Meals

On Day 1 and Day 28, subjects will fast overnight for at least 8 hours, will take CRV431 or matching placebo and will fast for an additional 2 hours after administration of study drugs. On subsequent days, subject will fast overnight for at least 8 hours, will take CRV431 or matching placebo and will fast for an additional 30 minutes after administration of study drugs.

7.5. COVID-19 Vaccine

Hepion in no way wishes to preclude subjects from receiving the COVID-19 vaccine. However, in order to minimize potential adverse events associated with the vaccine, if possible, the subject should try to receive their second dose of the vaccine seven days prior to the commencement of receiving study drug (Day 1) or receive their first dose of the vaccine 96 hours after their last dose on Day 28.

Enrolled study subjects who have an opportunity to be vaccinated against COVID-19 should do so. Study subjects will be permitted to continue on the study if they receive the COVID-19 vaccine.

The COVID-19 vaccine should be recorded in the subject's Concomitant Medications CRF page if the subject receives the vaccine after consent and through Day 42/EOS.

7.6. Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will monitor the trial. The DSMB will comprise of medical professionals with expertise in NASH and clinical trials and are external to the Sponsor. The DSMB will meet periodically or as needed to review accumulating safety data and any available PK data collected throughout the trial.

Safety and available PK data will be reviewed by the DSMB prior to proceeding with the next higher dose cohort. The DSMB will review safety data when at least six (6) subjects in Cohort A (CRV431 75 mg) and at least three (3) subjects in Cohort B (matching placebo) have reached 28 days of dosing, as described in Section 12.3.1. The DSMB will also review the Day 28 safety data from the remaining subjects to confirm there are no changes to the prior safety assessment.

The roles and responsibilities will be further defined in a Charter.

7.7. Safety Criteria for Adjustment or Stopping Doses

7.7.1. Individual Subject Criteria

If any of the criteria below are met by an individual subject, then no further dosing will occur at any of the study sites until a review of all available safety information is performed by the DSMB, Medical Monitor, and Sponsor. Appropriate Regulatory Agencies and Ethics Committees will be informed as applicable. If it is later determined that further dosing can be performed safely then an application for a substantial protocol amendment will be submitted to the appropriate Regulatory Agencies and Ethics Committees, if applicable. Stopping criteria for an individual subject includes:

- Grade 3 or higher CTCAE AEs possibly or probably related to study drug as determined by the investigator and sponsor;
- Grade 4 CTCAE AEs regardless of relation to study drug as determined by the investigator and sponsor;
- Any SAEs thought to be related to the study drug as determined by the investigator and sponsor.

For subjects experiencing any hepatic AEs or SAEs judged by the investigator or sponsor to be related to study drug, the investigator, DSMB, Medical Monitor and Sponsor will review all available safety data and make a determination to proceed with one of the following options:

- If the event was a drug-induced liver injury (DILI), considered as increases in aminotransferases (AT) >3 x ULN or >3 x baseline where baseline is defined as the average values of Screening and Day -1, no additional subjects will be dosed until it is determined that it is safe to proceed and in addition the frequency of blood chemistries will increase to daily, if appropriate.

  - Repeat testing of ALT, AST, ALP, TBL will be performed within 48-72 hours to confirm the abnormality.
  - If there are persistent elevations of AT > 3 x ULN or a 2-fold increase above baseline values (for those subjects with elevated values prior to drug exposure) upon repeat testing then close observation visits should be implemented and/or discontinuation of drug should be considered. Close Observations are described in Section 7.8.

- If the event was not a DILI, as defined above, one of the following actions will be taken:
  - Dose an entire additional cohort at the same or lower dose than the dose taken by the subject that experienced the event in question;
  - Continue to pause the study, until it is determined, that it is safe to proceed.

A decision to discontinue or temporarily interrupt the study drug for a subject will be considered based on following criteria:

- If ALT/AST baseline measurements (BLM) are <2 x ULN, discontinue if ALT or AST increases to >5 x BLM;
- If ALT/AST BLM ≥2 x ULN but <5 x ULN, discontinue if ALT or AST increases to 3 x BLM;
- If ALT/AST BLM ≥5 x ULN, discontinue if ALT or AST increases to >2 x BLM AND the increase is accompanied by a concomitant increase in TBL to >2 x BLM OR the International Normalized Ratio (INR) concomitantly increases by >0.2;
- Any subjects with signs and symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, and/or rash, accompanied by a >5% increase in eosinophils;
- Subjects who miss more than 2 consecutive QD doses of study drug. Subjects may be replaced unless a stopping rule precludes replacement.

7.7.2. Study Criteria

Dosing of study drug within the study will be stopped and recruitment into the study will be paused until a review of all available safety information is performed by the DSMB, Medical Monitor, and Sponsor if any of the following occur:

- ≥3 subjects in the study experience an SAE that is judged to be related to study drug by the investigator and sponsor;
- ≥3 subjects in the study experience a Grade 3 or Grade 4 CTCAE AE in the same system organ class (SOC) that are judged to be related to study drug by the investigator and sponsor;
- ≥3 subjects in the study experience a Grade 3 or Grade 4 CTCAE laboratory abnormality that are judged to be related to study drug by the investigator and sponsor. Asymptomatic elevations in cholesterol or triglycerides accepted;
- ≥3 subjects in the study experience a confirmed:
  - Friderica's QT Correction Formula (QTcF) interval ≥500 msec;
    OR

  - QTcF interval change from baseline ≥60 msec that has an absolute value ≥ 480 msec;
    - The value of an individual ECG time point is the average of the triplicate values
    - "confirmed" is defined as the abnormality duplicated, at least 1 hour after the abnormality is first noted, by the results of a set of 3 ECGs performed in triplicate, at least 5, but not more than 10 minutes between each assessment.
- ≥1 subject with AT >3 x ULN or >3 x subject baseline that is confirmed, not initially cholestatic, and judged to be adversely related to study drug (DILI) by the investigator and sponsor.

7.7.2.1. Study Stopping Criteria

Study will be stopped and a review of all available safety information is performed by the DSMB, Medical Monitor, and Sponsor if any of the below criteria is met:

- ≥1 subject develops a Grade 5 CTCAE adverse event attributed to CRV431
- ≥2 subjects develop a Grade 4 CTCAE adverse event attributed to CRV431
- ≥3 subjects develop the same Grade 3 CTCAE adverse event attributed to CRV431

The study may be restarted depending on the specific AE, relationship to the study drug and with the agreement of the DSMB, Medical Monitor and Sponsor.

7.7.3. Pharmacokinetic Criteria for Dose Adjustment

Dose adjustment is not available for subjects in Cohort A receiving 75 mg of CV431 QD. If a patient demonstrates adverse events that trigger the need for stopping, that patient will be stopped and an additional patient will be started on the same dose unless the study data indicates a problem with the dose level as recommended by the DSMB. Subjects in Cohort C, receiving 225 mg of CRV431 QD, experiencing a drug exposure related Grade 3,4 or 5 CTCAE can have a dosage reduction to 150 mg of CRV431 once daily.

7.8. Close Observation

Upon detection and confirmation of early signs of possible DILI (see Section 7.7.1), close observation should be initiated immediately.

Close observation will include the following:

- Repeating liver enzyme and serum bilirubin tests 2 or 3-times weekly. The frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic;
- Obtaining a more detailed history of symptoms and prior or concurrent diseases;
- Obtaining a history of concomitant drug use including non-prescription medications and herbal and dietary supplement preparations, alcohol use, recreational drug use, and special diets;

- Ruling out acute viral hepatitis types A, B, C, D, and E, autoimmune or alcoholic hepatitis, hypoxic/ischemic hepatopathy, and biliary tract disease;
- Obtaining a history of exposure to environmental chemical agents;
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin);
- Consider gastroenterology or hepatology consultations;
- Consider liver biopsy.

7.9. Criteria for Study Termination

Conditions may arise during the study that could prompt the study to be halted. Conditions that may prompt such considerations include, but are not limited to, the following:

- The discovery of unexpected, serious, or unacceptable risk to subjects enrolled in the study;
- A decision on the part of the sponsor or regulatory authority to suspend, discontinue, or shorten the study
- Study conduct at a study site may warrant termination under conditions that include the following:
  - Failure of the site to enroll eligible subjects into the study;
  - Failure of the investigator to comply with FDA, country-specific, or local regulations;
  - Submission of false information from the research facility to the sponsor, the clinical Monitor, or a regulatory authority;
  - Insufficient adherence to protocol requirements;
  - A conflict of interest on the part of the investigator, his/her institution, or site personnel that would negatively impact the integrity of the clinical trial;
  - Institution, site, investigator, or IRB/ICE under investigation for cause by a regulatory agency.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study.

1. Capable of giving written informed consent and able to effectively communicate with the investigator and study personnel. A signed ICF must be on file prior to initiating the Screening procedures;
2. Willing and able to complete all study requirements, restrictions, visits and procedures;
3. [redacted]
5. Male or female between 18 and 75 years of age (inclusive);
6. Females of reproductive potential, defined as women who have not been postmenopausal for at least 24 consecutive months (i.e., who have had menses within the preceding 24 months), or women who have not undergone surgical sterilization; specifically, hysterectomy, bilateral salpingectomy, bilateral oophorectomy, hysteroscopic sterilization, and/or tubal ligation, must have a negative pregnancy test at Screening and within the 24-hour period prior to Day 1;
7. All participants must agree not to participate in a conception process (i.e., active attempt to become pregnant or to impregnate, sperm or egg donation, in vitro fertilization). If participating in sexual activity that could lead to pregnancy, the participant must agree to use 2 reliable methods of contraception simultaneously while receiving study treatment and for 3 months after subject has stopped taking study drug. A combination of TWO of the following methods MUST be used appropriately:
    a. Condoms (male or female) with or without a spermicidal agent;
    b. Diaphragm or cervical cap with spermicide;
    c. IUD;
    d. Hormonal-based contraception.

    Note: Participants who are not of reproductive potential (women who have been postmenopausal for at least 24 consecutive months or have undergone hysterectomy, bilateral salpingectomy, bilateral oophorectomy, hysteroscopic sterilization, and/or tubal ligation, or men who have documented azoospermia) are eligible without requiring the use of contraceptives. Acceptable documentation of sterilization, menopause or male partner's azoospermia must be provided; serum follicle stimulating hormone (FSH) measurement can be used to document menopausal status.

8.2. Subject Exclusion Criteria

Subjects who meet the following criteria prior to the first dose of study drug are not eligible for randomization.

1. Pregnant or breastfeeding or planning to become pregnant during the study period;
2. Known allergy to CRV431, cyclosporine, or any of their inactive ingredients;
3. Positive test for HBsAg, HCVAb or HIVAb. If HCVAb test is positive, then an HCV-RNA test will be performed. If the HCV-RNA test is negative, the subject is allowed to participate in the study, as long as the subject meets all other inclusion criteria and has never been treated for HCV or was treated >2years ago and achieved a sustained virologic response at that time;
4. History of or any current medical condition which could compromise the safety of the participant in the study, as determined by the investigator;
5. Subjects with a systolic pressure >150 or a diastolic pressure >90. At the discretion of the investigator, the blood pressure may be re-measured after 10 minutes to ensure the blood pressure is in fact out of range. Out of range blood pressure after the second measurement will exclude a subject. If a subject has a blood pressure within the desired range due to anti-hypertension medication, that subject can be included at the discretion of the investigator, provided the anti-hypertension medication is not a contraindicated medication. Please refer to Appendix A for a list of drugs considered contraindicated;
6. Clinically significant gastrointestinal, cardiovascular, neurologic, psychiatric, metabolic, renal, hepatic, respiratory, inflammatory, or infectious disease, as determined by the investigator;
7. Subjects with a history of clinically significant acute cardiac event within 6 months prior to Screening such as stroke, transient ischemic attack, or coronary heart disease (angina pectoris requiring therapy, myocardial infarction, revascularization procedures, with LVEF <50% as determined by previous echocardiography or MUGA scan);
8. Subjects with uncontrolled or unstable cardiac arrhythmias:
    a. Severe conduction disturbance (e.g., second- or third-degree AV block);
    b. QTc interval >450 msec (males) or >470 msec (females);
    c. History of congenital long QT syndrome, congenital short QT syndrome, Torsades de Pointes, or Wolff Parkinson White syndrome;
9. Subjects with transaminases >5 x ULN and with ALP >2 x ULN;
10. Subjects with total serum bilirubin >1.5 x ULN, unless the subject has Gilbert's Syndrome, in which case the subject can be enrolled provided the direct bilirubin is within 30% of the TBL;
11. Subjects with a platelet count <150,000/m^3;
12. Systemic immunosuppression within 6 months prior to the first dose of study drug apart from short-term treatment for asthma, COPD or other respiratory conditions;

13. Current clinically significant diarrhea or gastric stasis that, in the investigator's opinion, could influence drug absorption or bioavailability;
14. Subject with any history or presence of decompensated cirrhosis;
15. Other well documented causes of chronic liver disease according to standard diagnostic procedures including, but not restricted to:
    a. Suspicion of drug-induced liver disease;
    b. Alcoholic liver disease;
    c. Autoimmune hepatitis;
    d. Wilson's disease;
    e. Primary biliary cholangitis, primary sclerosing cholangitis;
    f. Genetic hemochromatosis (Homozygosity for C282Y or C282Y/H63D compound heterozygote);
    g. Known or suspected HCC;
    h. History or planned liver transplant, or current MELD score >15;
16. History of, or current evidence of, gallstones, gall bladder disease, cholestasis that has not been treated with cholecystectomy, or pancreatitis;
17. Subjects with HbA1c >9.5%. For subjects with an HbA1c >9.5% at the Screening Visit, a repeat test may be performed. A repeat HbA1c result >9.5% will lead to exclusion;
18. At Screening, an eGFR <60 mL/min/1.73 m^2 (calculated by the CKD-EPI method) and/or a KDIGO category of >G2;
19. Safety laboratory abnormalities at Screening which are clinically significant as determined by the investigator;
20. Weight loss of more than 5% within 3 months prior to randomization;
21. Current abuse of alcohol or illicit drugs, or history of alcohol or illicit drug abuse within the preceding 2 years, as determined by the investigator. History of excess alcohol intake as defined by ≥21 units of alcohol per week in males and ≥14 units of alcohol per week in females for 2 years prior to enrollment where a "unit" of alcohol is equivalent to 12-ounce beer, 4-ounce of wine, or 1-ounce shot of hard liquor;
22. A positive urine drug screen for drugs with a high potential for abuse (amphetamines, cannabinoids, opiates, cocaine, benzodiazepine) or alcohol test at Screening or Day -1. For benzodiazepine's only: positive results will be accepted if due to an approved prescription. For cannabinoids, opiates and cocaine: On a case by case basis, positive results will be evaluated by the Sponsor and Medical Monitor in order to determine the subject's eligibility to safely be included in the study;
23. Significant medical or psychiatric illness that would interfere with compliance and ability to tolerate treatment as outlined in the protocol;
24. Subjects who cannot be contacted in case of emergency;
25. Judgement by the investigator that the subject should not participate in the study if the subject is unlikely to comply with all study procedures and treatment;

26. Received an investigational drug or investigational vaccine or used an investigational medical device within 30 days prior to first dose of study drug;
27. Subjects who have used any drugs or substances known to be strong inhibitors or inducers of CYP3A4/5 and drugs whose major elimination pathway is the BSEP or OAT3, and drugs that are major substrates of the hepatic uptake transporters, OATP1B1 and OATP1B3 within 30 days prior to the first dose of study drug. (**NOTE**: Please refer to Appendix A for a list of drugs considered contraindicated. If there are questions, please contact the Sponsor);
28. Subjects with a history of organ transplantation. Corneal transplantation will be allowed.

Abnormal ECG or laboratory parameters may be repeated once, if in the opinion of the investigator, the results are due to technical factors or are inconsistent with the potential subject's medical evaluation.

Potential study subjects who met all inclusion and exclusion criteria for this study but who, for personal or administrative reasons, were not included in a study cohort may be re-screened if more than 30 days have passed since their previous screening. For these subjects, use of ELF or Pro-C3 results previously obtained for this study will be extended for an additional 30 days up to a total of 60 days. There are no restrictions on the number of re-screens permitted for these subjects.

Potential study subjects who previously screened and failed only ELF or only Pro-C3 but met all other inclusion criteria and met none of the exclusion criteria for this study may be re-screened.

8.3. Subject Withdrawal Criteria

8.3.1. Early Termination of Subjects from the Study

Subjects who discontinue the study should complete all scheduled safety assessments at the Early Termination Visit. If an Early Termination Visit and a scheduled visit coincide, procedures for both visits should be completed, without duplication. Subjects must discontinue the study for the following reasons:

- Subject withdraws consent;
- Subject unwilling or unable to follow study procedures, per judgment of the investigator;
- Investigator, sponsor, or Regulatory Authority judge that further dosing with study drug would be harmful to the subject;
- Subject experiences an SAE that is judged, by the investigator and the sponsor, to be related to study drug;
- Subject experiences a Grade 3 CTCAE AE judged, by the investigator and the sponsor, to be related to study drug;
- Subject experiences a Grade 4 CTCAE AE judged, by the investigator and the sponsor, regardless of the relation to study drug;
- Subject experiences a Grade 3 or Grade 4 CTCAE laboratory abnormality judged by the investigator and the sponsor, to be related to study drug except for asymptomatic elevations in cholesterol or triglycerides which are accepted;

- Subject with normal ALT and bilirubin at baseline who experiences confirmed, non-cholestatic ALT >3 x ULN and bilirubin >2 x ULN OR subjects with elevated ALT at baseline who experiences confirmed, non-cholestatic ALT >10 x baseline value and bilirubin >2 x ULN;
- Subject experiences a confirmed,
  - QTcF interval 500 msec;
    OR
  - QTcF interval change from baseline ≥60 msec that has an absolute value ≥480 msec. The value of an individual ECG time point is the average of the triplicate values
  - "confirmed" is defined as the abnormality duplicated, at least 1 hour after the abnormality is first noted, by the results of a set of 3 ECGs performed in triplicate, at least 5, but not more than 10 minutes between each assessment;
- Subject experiences any hepatic AE or SAE judged by the investigator or sponsor as DILI and to be related to study drug and not to the subject's underlying NASH.

Subjects who discontinue the study due to the safety stopping criteria will be replaced if the investigator and sponsor agree and the criteria outlined in Section 7.5 are not violated. Subjects who discontinue the study for non-safety reasons may be replaced.

If a subject is withdrawn from the study the reason(s) for withdrawal must be documented in the subject's medical record and CRF. An Early Termination Visit should be performed. All subjects must be followed for safety until the time of the follow-up evaluation or until study drug related toxicities resolve, return to baseline or are deemed irreversible, whichever is longer.

Subjects who cannot be reached after 3 documented attempts to be contacted to schedule a follow-up visit will be considered lost to follow up.

8.4. Subject Replacement

Subjects who do not complete the study may be replaced, at the sponsor's discretion to ensure that the study is fully populated, unless a stopping rule precludes replacement. Replacement subjects will receive the same treatment assignment as the subject they are replacing. Each enrolled subject may only participate in this study once. The study is designed to have 12 subjects on active treatment and 6 subjects on placebo to complete the study.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1 Investigational Product

The investigational drug product, CRV431, is supplied as 75 mg softgel capsules without marking. The study drug details are presented in Table 4.

Table 4 Investigational Product

	Investigational Product
Product Name:	CRV431 active pharmaceutical ingredient
Dosage Form:	Softgel capsule
Unit Dose	75 mg
Route of Administration	PO
Physical Description	[redacted]

9.2 Placebo

The placebo for this study utilizes the same formulation, white opaque, oblong softgel capsule without marking and without the active ingredient of CRV431 drug substance.

9.3 Study Drug Packaging and Labeling

Study supply will be packaged in blister packs, containing 6 softgel capsules per pack. All study supplies will be labeled as "New Drug – Limited to United States Federal Law to Investigational Use."

9.4 Study Drug Storage

CRV431 softgel capsules and placebo should be stored between 20°C to 25°C or 68°F to 77°F. Excursions are permitted to 15°C to 30°C or 59°F to 86°F.

9.5 Study Dug Preparation

No preparation will be required for the CRV431 softgel capsules.

9.6 Study Drug Accountability

The Investigator or their designee, must maintain accurate records demonstrating dates and amount of drug received, in what condition the drug was received, to whom it was dispensed (subject-by-subject accounting) and must account of any drug accidentally or deliberately destroyed.

Drug accountability should be completed for CRV431 and placebo during this study.

9.7 Study Drug Handling and Disposal

During the treatment period of the study, CRV431or placebo will be supplied by a pharmacist or investigator designee responsible for study drug administration and accountability. On study visit days, treatment may only be administered under the supervision of the investigator or site designee(s).

Any used, expired, or non-usable study drug can be destroyed on-site as per the sites standard operating procedures with approval of the sponsor. If study drug cannot be destroyed on-site, it must be returned to the sponsor or designee.

10. PHARMACOKINETIC ASSESSMENTS

10.1. Blood Sample Collection

Whole blood collection procedures are outlined in the Laboratory Procedures Manual. Collection times for PK sampling periods are outlined in Table 6.

10.2. Sample Handling and Shipment

Instructions for specimen sampling, handling, and shipment are provided in the Laboratory Procedures Manual. Samples may be stored for up to 20 years.

10.3. Sample Analysis

Whole blood PK samples will be analyzed for the quantitative concentrations of CRV431 using a validated liquid chromatography/tandem mass spectroscopy (LC–MS/MS) assay. Qualitative analysis will also be performed on the whole blood PK samples of CRV431 for its major metabolites.

10.4. Whole Blood Pharmacokinetic Parameters

Pharmacokinetic parameters for the measurement of CRV431 and its metabolites will be performed from whole blood and are shown in Table 5.

Table 5: Pharmacokinetic Parameters

Parameter	Definition
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted] No PK parameters will be calculated for subjects with 2 or fewer consecutive time points with detectable concentrations. Individual and mean whole blood concentration time curves (both linear and log-linear) will be [redacted]

Table 6: Pharmacokinetic Sampling Schedule

Day	**Day 1**				**Day 14**	**Day 28**			
Time (h)	Pre-dose	2.0	4.0	8.0	312 (Pre-dose)	Pre-dose	2.0	4.0	8.0
Whole blood (PK)	X	X	X	X	X	X	X	X	X
Plasma (f_u)	X	X				X	X		

Abbreviations: f_u, fraction unbound; h, hour; PK, pharmacokinetic(s).

11. ASSESSMENT OF SAFETY

11.1. Safety Parameters

11.1.1. Demographic

Demographic details will be collected at Screening only.

11.1.2. Vital Signs

Vital sign assessments will comprise of blood pressure, heart rate, temperature, and respiratory rate measurements. Blood pressure will be measured with a standard mercury sphygmomanometer or an automated oscillometric blood pressure monitor, after the subject has been resting in a supine position for at least 5 minutes. Heart rate will be measured by an automated vital signs machine. Respiratory rate will be measured only if medically indicated. Vital signs will be performed for all subjects at the time points indicated in Table 3, or as applicable.

11.1.3. Weight and Height

Weight and height will be assessed at the Screening visit only.

11.1.4. Physical Examination and Medical History

Physical examinations will be performed at Screening. Additional examinations may be performed throughout the study, if considered medically necessary. The examinations will include the following body systems: general appearance; eyes, ears, nose, and throat; head and neck; chest and lungs; cardiovascular; abdomen; musculoskeletal; lymphatic; dermatologic; neurologic; psychiatric; and extremities.

A detailed medical history will be collected at the Screening visit only.

11.1.5. Electrocardiogram

Twelve-lead ECGs will be performed after the subject has been supine for 5 minutes, and 1½ to 3 hours after the morning dose. On Day 1 and Day 28, ECGs will be performed prior to the 2 hr. PK draw. Electrocardiograms performed on non-dosing Days should be completed within the same time window as the ECGs that were done 1½ to 3 hours after the time the morning doses were administered. These ECG schedules will therefore be close to the time of day the previous post-dose ECGs were obtained. The timing of the ECG may be adjusted to C_{max} values as new data becomes available. All ECGs should be interpreted by the investigator or qualified designee within 12 hours of the time the ECGs were performed. Electrocardiograms will be performed for all subjects at the time points indicated in Table 3, or as applicable.

11.1.6. Laboratory Assessments

All samples should be collected and shipped as directed in the Laboratory Procedures Manual.

Routine clinical laboratory testing will be performed for all subjects at the time points indicated in Table 3, or as applicable. Samples may be stored up to 20 years.

If the investigator believes that access to laboratory data is medically indicated and that a delay in access to central laboratory safety results would pose a potential safety risk to the subject, the sample will be split; a portion will be sent to the local laboratory for appropriate laboratory tests, and the other portion will be sent to the central laboratory for routinely scheduled testing.

Samples will be collected and stored for testing for additional safety or PK testing as necessary.

11.1.6.1. Hematology and Coagulation

Samples will be collected before study drug dosing and after at least an 8-hour fast; however, in case of an early termination or recheck, subject fasting is not required prior to sample collection. The following will be performed:

- Total white blood cell (WBC) count differential (absolute values)
- Hematocrit
- Hemoglobin
- Red blood cell (RBC) distribution width
- Mean corpuscular hemoglobin concentration
- Mean corpuscular hemoglobin
- Mean corpuscular volume
- Platelet count
- Prothrombin time with INR
- RBC count

11.1.6.2. Blood Chemistry

Samples will be collected before study drug dosing and after at least an 8-hour fast; however, in case of an early termination or recheck, subject fasting is not required prior to sample collection. The following tests will be performed:

- ALT
- Albumin
- ALP[a]
- Amylase, total[a] or pancreatic amylase
- Anion gap
- AST
- Bicarbonate
- Bilirubin (total, unconjugated, conjugated)
- Blood urea nitrogen
- Calcium
- Chloride
- Cholesterol (total, high-density lipoprotein [HDL], and low-density lipoprotein [LDL])
- Creatinine
- Creatine kinase[b]
- eGFR, using CKD-EPI method
- Glucose
- HbA1c[c]
- Lipase
- Phosphorus
- Potassium
- Sodium
- Triglycerides

a Reflex fractionation, if greater than ULN

b Reflex fractionation if greater than critical value

c HbA1c will be collected at Screening, D28, EOS and ET

Subjects with normal ALT and bilirubin at baseline who have ALT >3 x ULN and bilirubin >2 x ULN OR subjects with elevated ALT at baseline who have ALT > 10 x baseline value and bilirubin >2 x ULN will also have serum gamma-glutamyltransferase (GGT) determined at the time these abnormalities are discovered. For these subjects, GGT may be repeated, as clinically indicated.

11.1.6.3. Urinalysis

Samples will be collected before study drug dosing and after at least an 8-hour fast; however, in case of an early termination or recheck, subject fasting is not required prior to sample collection. The following will be performed:

- Bilirubin
- Blood
- Color
- Glucose
- Ketones
- Leukocyte esterase
- Nitrites
- pH
- Protein
- Specific gravity
- Turbidity
- Urobilinogen
- Microscopic examination[a]

[a] Microscopic examination will be performed if dipstick test is positive for protein, blood, leukocyte esterase, or nitrites. (Microscopic examination includes bacteria, casts, crystals, epithelial cells, RBCs, and WBCs).

11.1.6.4. Drug Screen

A standard screen for drugs of abuse which includes testing for amphetamine, cannabinoids, opiates and cocaine will be performed for all subjects at the time points indicated in Table 3, or as applicable.

11.1.6.5. Pregnancy Screen

Females of reproductive potential defined as women who have not been postmenopausal for at least 24 consecutive months (i.e., who have had menses within the preceding 24 months), or women who have not undergone surgical sterilization; specifically, hysterectomy, bilateral salpingectomy, bilateral oophorectomy, hysteroscopic sterilization, and/or tubal ligation, must have a negative pregnancy test at Screening, within the 24 hour period prior to Day 1 and at all other time points indicated in Table 3, or as applicable. At Screening a serum beta human chorionic gonadotropin or urine dipstick pregnancy test will be performed. A urine dipstick pregnancy test will be performed at all other time points.

All post-menopausal females will have an FSH test at Screening.

11.2. Adverse and Serious Adverse Events

11.2.1. Adverse Events

An AE is defined as any untoward medical occurrence in a clinical study subject associated with the use of a drug (investigational or non-investigational) in humans, whether or not considered drug related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory

finding), symptom, or disease temporally associated with the use of a drug, without any judgement on causality. An AE can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including overdose.

All AEs that occur after any subject has been consented, before treatment, during treatment, or up to and including the End of Study or Early Termination Visit, whether or not they are related to the study, must be recorded on forms provided by Hepion.

11.2.2. Serious Adverse Events

An AE is considered serious if, in the view of either the investigator or sponsor, it fulfills at least one of the following:

- Results in death;
- It is immediately life-threatening;
- It requires in-patient hospitalization or prolongation of existing hospitalization;
- It results in persistent or significant disability or incapacity;
- Results in a congenital abnormality or birth defect;
- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

All SAEs that occur after any subject has been consented, before treatment, during treatment, or up to and including the End of Study or Early Termination Visit, whether or not they are related to the study, must be recorded on forms provided by Hepion.

11.2.3. Other Adverse Events

Other AEs will be identified by the investigator and if applicable also by the medical monitor during the evaluation of safety data for the Clinical Study Report. Adverse events of special interest, other than SAEs or AEs leading to discontinuation of the subject from the study, will be classified as other AEs. For each of these other AEs, a narrative may be written and included in the Clinical Study Report.

11.3. Relationship to Study Drug

An investigator who is qualified in medicine must make the determination of relationship to the investigational product, when appropriate, for each AE (unrelated, possibly related or probably related). The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as “unrelated.” If there is any valid reason, even if undetermined, for suspecting a possible cause and effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related.”

If the relationship between the AE/SAE and the investigational product is determined to be “possible” or “probable” the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

11.4. Recording Adverse Events

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Clinically significant changes in laboratory values, blood pressure, and pulse requiring an intervention should be reported as AEs. The AE term should be reported in standard medical terminology when possible. For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), severity, causality, action taken, serious outcome (if applicable), and whether or not it caused the subject to discontinue the study.

Adverse events should be collected and recorded in the source documents and on the eCRF beginning at the time of signing the informed consent. Adverse events and SAEs should be reported through End of Study Visit or Early Termination Visit. Both AEs and SAEs should be followed until resolution/stabilization or until a time that is mutually agreed upon between the medical monitor and investigator.

Subjects who experience any AE or SAE should receive appropriate treatment and medical supervision as clinically indicated.

All AEs will be graded for severity according to the Common Terminology Criteria for Adverse Events table v5.0 (CTCAE, 2017).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 11.2.2. An AE of severe intensity may not be considered serious.

Should a pregnancy occur, it must be reported and recorded on Hepion's pregnancy form. Pregnancy, in itself, is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

11.5. Reporting Adverse Events

Serious adverse events must be reported to the Sponsor within 24 hours of the investigator becoming aware of the event along with an assessment of causality. If at the time the investigator submits an initial SAE report and the SAE has not been resolved, the investigator must provide a follow-up report as soon as the event resolves (or upon receipt of significant information if the event is still ongoing). Additional follow-up information, if required or available, should reported to the Sponsor within one business Day of receipt. This should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the CRF and/or study file.

All SAEs must be followed until resolution/stabilization or until a time that is mutually agreed upon between the Medical Monitor and the Investigator.

Hepion (or representative) is responsible for notifying the relevant regulatory authorities of certain events. It is the Investigator's responsibility to notify the IRB or IEC of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events that occur during the clinical trial. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

12. STATISTICS

12.1. Sample Size Determination

The sample size selected for each population to evaluate the effect of NASH F2/F3 on the PK of CRV431 was not chosen to satisfy any *a priori* statistical requirement. This sample size of a total of 36 subjects (12 active with 6 matching placebo at each dose level) has historically been shown to be sufficient for studies of this type and should provide adequate data to support the planned analyses.

12.2. Population for Analyses

12.2.1. Pharmacokinetic Population

Samples from all subjects will be assayed even if the subjects do not complete the study. All subjects who comply sufficiently with the protocol and display an evaluable PK profile (e.g., exposure to treatment, availability of measurements and absence of major protocol violations) will be included in the statistical analyses.

12.2.2. Safety Population

All subjects who received the study drug or placebo will be included in the safety evaluations.

12.3. Statistical Analyses

12.3.1. Interim Safety Review

An interim safety review will be performed when at least six (6) subjects in Cohort A (CRV431 75 mg) and at least three (3) subjects in Cohort B (matching placebo) have reached 28 days of dosing. A minimum of 28 days of safety data and any available PK data will be reviewed by an independent DSMB. Dosing of Cohort C (CRV431 225mg) and Cohort D (matching placebo) may proceed if agreement of the DSMB has been received and no stopping rules have been met. The DSMB will also review the Day 28 safety data from the remaining subjects to confirm there are no changes to the prior safety assessment. For the purpose of the interim safety review, dosing in Cohort A and Cohort B will not be paused during this DSMB review.

12.3.2. Analysis of Covariance

Placebo subjects will be used for comparison with all presumed NASH treatment subjects using the following analysis.

An analysis of covariance (ANCOVA) will be performed on the ln-transformed $AUC_{0\text{-}inf}$ and C_{max}. The ANCOVA model will contain a categorical factor of population (for subjects with F2/F3 presumed NASH, and F2/F3 presumed NASH placebo subjects), a categorical covariate (sex), and continuous covariates (age, weight, BMI and ideal body weight).

The comparisons of interests are:

- CRV431-treated F2 presumed NASH subjects versus placebo treated F2 presumed NASH subjects stratified by dosing cohort, i.e. Cohort A (75 mg QD) versus Cohort C (225 mg QD);
- CRV431-treated F3 presumed NASH subjects versus placebo treated F3 presumed NASH subjects stratified by dosing cohort, i.e. Cohort A (75 mg QD) versus Cohort C (225 mg QD);
- CRV431-treated pooled F2/F3 presumed NASH subjects versus pooled placebo treated F2/F3 presumed NASH subjects stratified by dosing cohort will only be evaluated for differences i

A full covariate population PK/PD model will be developed for exploratory purposes.

12.3.3. Ratios and Confidence Intervals

Ratios of least-squares means (LSM) will be calculated using the exponentiation of the difference between F2/F3 presumed NASH groups LSM from the analyses on the ln-transformed

$AUC_{0\text{-}inf}$ and C_{max}. These ratios will be expressed as a percentage relative to the F2/F3 presumed NASH placebo control group.

Ninety percent (90%) confidence intervals (CIs) for the ratios will be derived by exponentiation of the CIs obtained for the difference between F2/F3 presumed NASH groups LSM resulting from the analyses on the ln-transformed $AUC_{0\text{-}inf}$ and C_{max}. The CIs will be expressed as a percentage relative to the F2/F3 presumed NASH placebo control group.

12.3.4. Pharmacokinetics Analyses

Values will be calculated for the whole blood concentrations and the PK parameters listed in Section 10.4, using appropriate summary statistics to be fully outlined in the SAP. Population PK/PD analysis will be used to explore PK dependent covariates and quantitative concentration-effect relationships.

12.3.5. Safety Analyses

All safety data will be populated in the individual CRFs. All safety data will be listed by subjects.

Adverse events will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) summarized by treatment for the number of subjects reporting the treatment emergent adverse event (TEAE) and the number of TEAEs reported. A by-subject AE data listing including verbatim term, coded term, treatment, severity, and relationship to population will be provided.

Safety data including ECGs, vital signs assessments and clinical laboratory results, will be summarized by population and point of time of collection.

Descriptive statistics using appropriate summary statistics will be calculated for quantitative safety data as well as for the difference to baseline, when appropriate. In addition, a shift table describing out of normal range shifts will be provided for clinical laboratory results.

Concomitant medications will be listed by subject and coded using the most current version of WHO drug dictionary. Medical history will be listed by subject.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring

Before an investigator can enter a subject into the study, Hepion (or representative) may visit the investigational study site to:

- Determine the adequacy of the facilities;
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Hepion (or representative). This will be documented in a Clinical Study Agreement between Hepion (or representative) and the investigator.

During the study, a monitor from Hepion (or representative) will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s);
- Confirm that facilities remain acceptable;
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the CRF, and that investigational product accountability checks are being performed;
- Perform source data verification. This includes a comparison of the data in the CRF with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts);
- Record and report any protocol deviations not previously sent to Hepion (or representative);
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to Hepion (or representative) and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

13.2. Audits and Inspections

Authorized Hepion employee (or representative), regulatory authority personal, or members of IEC or IRB may visit the site to perform audits or inspections including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice, guidelines of the International Conference on Harmonization , and any applicable regulatory requirements. The investigator should contact Hepion immediately if contacted by a regulatory agency about an inspection.

13.3. Institutional Review Board

The investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the subject consent form and recruitment materials must be maintained by the investigator and made available for inspection.

14. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practice and all applicable regulatory requirements, Hepion (or representative) may conduct a quality assurance audit. Please see Section 13.2 for more details regarding the audit process.

15. ETHICS

15.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved, or given a favorable opinion in writing by an IRB or IEC as appropriate. The investigator must submit written approval to Hepion (or representative) before he or she can enroll any subject into the study.

The investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Hepion (or representative) will provide this information to the investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

15.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization /Good Clinical Practice, and applicable regulatory requirements.

15.3. Written Informed Consent

The investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject’s signed and dated informed consent must be obtained before conducting any study procedures.

The investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

16. DATA HANDLING AND RECORDKEEPING

16.1. Inspection of Records

Hepion (or representative) will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

16.2. Retention of Records

The investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Hepion (or representative) or the Regulatory Authority to review any documentation relating to the study, the investigator must permit access to such records.

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18. APPENDICES

APPENDIX A. CONTRAINDICATED DRUGS

CYP3A4/5: Inhibitors			
Enzyme	**Strong inhibitors**	**Moderate inhibitors**	**Weak inhibitors**
CYP3A	boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole clarithromycin, diltiazem, idelalisib, nefazodone, nelfinavir	aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil	amiodarone, chlorzoxazone, cilostazol, fosaprepitant, istradefylline, ivacaftor, lomitapide, ranitidine, ranolazine, tacrolimus, ticagrelor

CYP3A4/5: Inducers			
Enzyme	**Strong Inducers**	**Moderate Inducers**	**Weak Inducers**
CYP3A	carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort	bosentan, efavirenz, etravirine, modafinil	armodafinil, rufinamide

Transporter Inhibitors		
Transporter	**Gene**	**Inhibitor**
OATP1B1, OATP1B3	*SLCO1B1, SLCO1B3*	atazanavir and ritonavir, clarithromycin, cyclosporine, erythromycin, gemfibrozil, lopinavir and ritonavir, rifampin (single dose), simeprevir
OAT1, OAT3	*SLC22A6, SLC22A8*	p-aminohippuric acid (PAH), probenecid, teriflunomide

AMBITION: A Phase 2A, Multi-Center, Single-Blind, Placebo-Controlled Study to Evaluate the Safety and Tolerability of CRV431 Dosed Once Daily in NASH induced F2 AND F3 Subjects

Protocol Number:	HEPA-CRV431-201
Protocol Version:	5.0
Protocol Date:	01 March 2021

NCT04480710

STATISTICAL ANALYSIS PLAN

Version 1.0

AMBITION: A Phase 2A, Multi-Center, Single-Blind, Placebo-Controlled Study to Evaluate the Safety and Tolerability of CRV431 Dosed Once Daily in NASH induced F2 AND F3 Subjects

STATISTICAL ANALYSIS PLAN

Version 1.0

Author: [redacted]

CTI Biostatistics Reviewer: [redacted]

Sponsor Approval: [redacted]

Hepion Pharmaceuticals, Inc.

[redacted]

Note that the last signature date is the effective date of the plan.

Table of Contents

LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical, Therapeutic, and Chemical
BMI	Body mass index
[redacted]	[redacted]
CRPM	C-reactive protein metabolite
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
F2	Fibrosis stage 2
F3	fibrosis stage 3
[redacted]	[redacted]
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
PK	Pharmacokinetics
[redacted]	[redacted]
PT	Preferred term
QD	Once daily
QTcF	Friderica's QT Correction Formula
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SI	International System of Units
SOC	System Organ Class
[redacted]	[redacted]

1. INTRODUCTION

This statistical analysis plan (SAP) is prepared in conjunction with the Hepion Pharmaceuticals, Inc.'s protocol number HEPA-CRV431-201 titled, "AMBITION: A Phase 2A, Multi-Center, Single-Blind, Placebo-Controlled Study to Evaluate the Safety and Tolerability of CRV431 Dosed Once Daily in NASH induced F2 and F3 Subjects" .

The primary purpose of this study is to evaluate the safety and tolerability and pharmacokinetics (PK) of CRV431 in subjects with presumed nonalcoholic steatohepatitis (NASH) F2/F3 fibrosis.

This SAP provides detailed description of the statistical methods specified in the protocol. An interim analysis will be performed when at least six (6) subjects in Cohort A (CRV431 75 mg) and at least three (3) subjects in Cohort B (matching placebo) have reached 28 days of dosing. The DSMB will also review the Day 28 safety data from the remaining subjects to confirm there are no changes to the prior safety assessment. The final planned analyses will be performed after database lock.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

- To evaluate the safety and tolerability of once daily (QD) 75 mg and 225 mg doses of CRV431 in presumed NASH fibrosis stage 2 (F2)/fibrosis stage 3 (F3) subjects compared to placebo control over 28 days of dosing
- To evaluate the pharmacokinetics (PK) of a QD dose of CRV431, its major metabolites and fraction unbound in presumed NASH F2/F3 subjects over 28 days of dosing.

2.1.2 Secondary Objectives

- To evaluate non-invasively the antifibrotic activity of a QD dose of CRV431. as measured by quantification of selected biomarkers of fibrosis, in presumed NASH F2/F3 subjects over 28 days of dosing.

2.1.3 Exploratory Objectives

- [redacted]

Metalloelastase], MMP-13 [Collagenase 3]) and tissue inhibitor of metalloproteinase

[redacted]

2.2 Endpoints

2.2.1 Study Endpoints

2.2.1.1 Safety Endpoints

Safety and tolerability parameters, including AEs, SAEs, AEs of special interest, physical examinations including weight and height, concomitant medications, laboratory assessments including blood chemistry, hematology and coagulation, urinalysis, pregnancy screening, ECG, and vital sign assessments, will be determined.

2.2.1.2 Pharmacokinetic Endpoints

The PK parameters for CRV431 in whole blood will be determined in subjects in fasted state. A list of PK parameters is shown in Table 5 in the protocol.

On an exploratory basis, concentration-effect relationships will be explored between CRV431 whole blood concentrations and all biomarkers measured. Subject demographics and clinical laboratory data will be evaluated as potential covariates in PK/PD model using non-linear mixed effect modeling with direct and indirect models.

2.2.2 Exploratory Endpoints

Assessments of biomarkers of collagen, lipidomics, and RNA sequencing.

3. INVESTIGATIONAL PLAN

3.1 Study Design

This is a randomized, single-blind, placebo-controlled, QD dose study of CR431 in presumed NASH F2/F3 subjects. This study will consist of 3 phases: (i) Screening and Randomization; (ii) treatment; and (iii) follow up.

3.1.1 Screening and Randomization Period

Screening visits will be conducted within 30 days prior to study Day 1.
Upon determination that a subject meets all eligibility criteria, the subject will be randomized on Study Day -1 to receive either CRV431 or matching placebo in a 2:1 subject ratio (12 CRV431 75mg to 6 matching placebo and 12 CRV431 225mg to 6 matching placebo).

Table 1: Study Design

Cohort*	Fibrosis Stage	N	Day 1 – 28, fasted oral dosing	Day 29 - 42
A	F2/F3	12	CRV431 75 mg	Observation/Follow up
B		6	Placebo[a]	
C		12	CRV431 225 mg	
D		6	Placebo[b]	
*Randomized assignment; 2:1 – CRV431: Placebo [a] Matching Placebo for Cohort A - 75 mg dose. [b] Matching Placebo for Cohort C - 225 mg dose.				

3.1.2 Treatment Period

Subjects will receive treatment with CRV431 or placebo from Day 1 to Day 28.

3.1.3 Follow Up Period

After completion of the treatment period, the subjects will be monitored for additional 14 days.

3.2 Treatment

Subjects in Cohort A will receive CRV431 75 mg (1 x 75 mg softgel capsule) QD and subjects in Cohort B will receive the matching placebo (1 x placebo softgel capsule) for Cohort A.

Subjects in Cohort C will receive CRV431 225 mg (3 x 75 mg softgel capsules) QD and subjects in Cohort D will receive the matching placebo (3 x placebo softgel capsules) for Cohort C.

3.2.1 Treatment Administration

Subjects will take study drug on the morning of each dosing day, with approximately 240 mL of water. On Day 1 and Day 28, subjects will fast overnight for at least 8 hours, will take CRV431 or matching placebo and will fast for an additional 2 hours after treatment administration. On subsequent days, subject will fast overnight for at least 8 hours, will take CRV431 or matching placebo and will fast for an additional 30 minutes after treatment administration.

3.2.2 Treatment Compliance

While in the Clinical Research Unit, study treatment will be administered under the supervision of site personnel. Compliance during the non-study visit days will be assessed by subject report

and pill count. A qualified designee will be responsible for monitoring the administration of the timed oral doses on study visit days.

4. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

Unless otherwise specified, continuous variables will be summarized by presenting the number of non-missing observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by presenting the number of subjects and percentages for each category.

All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum will be formatted to the same number of decimal places as the measured value.

Analyses will be performed using SAS for Windows statistical software, version 9.4 or higher (SAS, Cary, NC), except where other software may be deemed more appropriate.

4.1 Data Quality Assurance

Once all the source verification is complete, all queries are resolved, and the database has been updated appropriately, the database will be locked and made available to CTI Biostatistics for final analysis.

All SAS programs used to create analysis data sets, tables, listings, and figures are double programmed. The SAS outputs will be compared, and the programs will be updated until the outputs match.

4.2 Analysis Sets

4.2.1 Pharmacokinetic Set

The Pharmacokinetic Set is defined as all subjects who comply sufficiently with the protocol and

display an evaluable PK profile (e.g., exposure to treatment, availability of measurements and absence of major protocol violations). Samples from all subjects will be assayed even if the subjects do not complete the study.

[redacted]

4.2.2 Safety Set

The Safety Set is defined as all subjects who received the study drug or placebo.

All safety analyses will be performed using the Safety Set.

4.3 Assessment Windows

For the purpose of listing and summarizing data, the time-in-study for each subject observation will be defined using study days as defined in the Schedule of Events (Appendix A). No analysis windows are planned for the study regarding data collected outside the protocol specified windows. All data will be included in the analysis based on the visit as it is recorded in the database.

4.4 Handling of Dropouts or Missing Data

Missing data will remain missing. No imputation of missing data will be performed.

4.5 Multiple Comparisons

There are no multiple comparisons.

4.6 Data Derivations and Transformations

Baseline is defined as the last non-missing value prior to the first dose of CRV431 or placebo administration.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

Subject disposition including subjects randomized, subjects in each analysis set, study completion status, and reasons for early discontinuations will be summarized by presenting frequency counts and percentages for each treatment group. A by subject listing will also be provided.

A listing of informed consent and eligibility will be provided for all subjects that signed informed consent.

5.2 Protocol Deviations

Distribution for the types of protocol deviations and the number of subjects that deviate from the protocol will be tabulated for the treatment group.

5.3 Demographic Characteristics

Demographic data, consisting of subjects who provided consent for collection of a genomic sample, age, sex, ethnicity, race, weight (kg), height (cm), and body mass index (BMI) assessed at screening visit will be summarized by treatment for the Safety Set.

5.4 Medical History

All medical conditions and surgical procedures will be classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percent of subjects with each medical condition and surgical procedure will be presented for each SOC and PT for the Safety Set.

5.5 Prior and Concomitant Medications

Concomitant medications will be coded using World Health Organization (WHO) drug classifications. The number and percent of safety subjects using concomitant medications will be tabulated by Anatomical, Therapeutic, and Chemical (ATC) class 4 and by preferred name.

5.6 Non-drug Therapies

Non-drug therapies will be classified by SOC and PT using MedDRA. The number and percent of subjects with each medical condition and surgical procedure will be presented for each SOC and PT for the Safety Set. The number and percent of subjects using non-drug therapies will be presented for each SOC and PT for the Safety Set.

6. EFFICACY ANALYSIS

6.1 Primary Efficacy Endpoint and Analysis

The endpoints of this study are safety and tolerability related and therefore there are no efficacy endpoints.

6.2 Pharmacokinetic Endpoints and Analysis

[redacted]

6.3 Exploratory Endpoints and Analysis

[redacted]

7. SAFETY ANALYSIS

All safety summaries (or analyses if applicable) will be conducted using the Safety Set.

7.1 Extent of Exposure

The duration of exposure, the total exposure of CRV431, the total number of doses and capsules will be summarized and presented by visit and overall. All data will be listed.

7.2 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical study subject associated with the use of a drug (investigational or non-investigational) in humans, whether or not considered drug related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgement on causality. An AE can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including overdose.

All AEs that occur after any subject has been consented, before treatment, during treatment, or up to and including the End of Study or Early Termination Visit, whether or not they are related to the study, must be recorded on forms provided by Hepion Pharmaceuticals, Inc.

7.2.1 Treatment-emergent Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an AE that occurs after study drug administration.

7.2.2 Adverse Event Severity

All AEs will be graded for severity according to the Common Terminology Criteria for Adverse Events table v5.0 (CTCAE, 2017).

7.2.3 Adverse Event Relationship to Study Medication

An investigator who is qualified in medicine must make the determination of relationship to the

investigational product, when appropriate, for each AE (unrelated, possibly related or probably related). The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause and effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related."

If the relationship between the AE/SAE and the investigational product is determined to be "possible" or "probable" the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

7.2.4 Serious Adverse Events

An AE is considered serious if, in the view of either the investigator or sponsor, it fulfills at least one of the following:

- Results in death
- It is immediately life-threatening
- It requires in-patient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

7.2.5 Adverse Event Summaries

All AEs (serious and non-serious) occurring after completion of the informed consent process and before the end of study, regardless of relationship to study drug, will be included and classified by SOC and PT using the Medical Dictionary for Regulatory Activities (MedDRA).

For treatment-emergent AEs (TEAEs), the following will be summarized and presented for the safety analysis set:

i. An overall summary of TEAEs, which includes:
   a. the number and percentage of subjects experiencing a TEAE
   b. the number and percentage of subjects experiencing a TEAE by strongest relationship to study medication
   c. the number and percentage of subjects experiencing a TEAE by greatest severity
   d. the number and percentage of subjects experiencing a TEAE leading to study withdrawal
   e. the number and percentage of subjects experiencing a treatment emergent SAE (TESAE)

ii. the number and percentage of subjects experiencing a TEAE by SOC and PT

iii. the number and percentage of subjects experiencing a TEAE by SOC, PT and the highest severity

iv. the number and percentage of subjects experiencing a TEAE by SOC, PT and the strongest relationship to study medication

v. the number and percentage of subjects experiencing a TESAE by SOC and PT

vi. the number and percentage of subjects experiencing a TEAE leading to study withdrawal by SOC and PT

In the overall summary of TEAEs table (i), besides tabulating the number and percentage of subjects, the total number of TEAE episodes will also be provided. If a subject has repeated episodes of a particular TEAE, all episodes will be counted in the summary table.

In the remaining summary tables, the incidence of TEAEs will be calculated by dividing the number of subjects who have experienced the event by the total number of subjects in the safety set. Thus, the incidence of TEAEs is shown in terms of the total number of subjects and not in terms of the total number of episodes. If a subject has repeated episodes of a particular TEAE, only the most severe episode, or the episode with the strongest causal relationship to study drug, will be counted in the summary tables.

A subject with more than one type of TEAE in a particular SOC will be counted only once in the total of subjects experiencing TEAEs in that particular SOC. Since a subject could have more than one type of TEAE within a particular SOC, the sum of subjects experiencing different TEAEs within the SOC could appear larger than the total number of subjects experiencing TEAEs in that SOC. Similarly, a subject who has experienced a TEAE in more than one SOC will be counted only once in the total number of subjects experiencing AEs in all SOCs.

All occurrences of all AEs will be listed for each subject, grouped by cohort. The listing will contain the following information: treatment group, verbatim term, SOC, PT, severity, relationship to study medication, date and day of onset, date and day of resolution, treatment given to treat the adverse event, the outcome, whether the event was an SAE, whether it led to withdrawal and whether it is a TEAE. Listings will be sorted by subject identification number, onset date, SOC, and PT. If the onset date is completely missing, then these events will be presented first. If the onset date is missing a month or a day, then these events will be presented before any complete dates.

7.3 Clinical Laboratory Assessments

Hematology, Coagulation, Blood Chemistry and Urinalysis data will be summarized by treatment group and visit. All clinical laboratory data will be converted to International System of Units (SI). Both raw and change from baseline values will be summarized by presenting the descriptive statistics by treatment group and visit.

Central and local drug and alcohol test results and pregnancy tests results will be listed.

7.4 Vital Signs

Vital signs raw and change from baseline values will be summarized by presenting the descriptive statistics of blood pressure, heart rate, temperature, and respiratory rate measurements by treatment group and visit.

7.5 ECG

The ECG measurements (PR Interval, Heart Rate, QRS Interval, QT Interval [uncorrected], and QTcF [Friderica's QT Correction Formula]) will be summarized by presenting descriptive statistics of raw data and change from baseline values by treatment group and visit.

7.6 Physical Examination

A listing of physical examination abnormalities will be provided.

8. DATA SAFETY MONITORING BOARD

An independent Data Safety Monitoring Board (DSMB) will monitor the trial. The DSMB will comprise of medical professionals with expertise in NASH and clinical trials and are external to the Sponsor. The DSMB will meet periodically or as needed to review accumulating safety data and any available PK data collected throughout the trial. See the DSMB Charter for details.

9. INTERIM ANALYSIS

10. SAMPLE SIZE AND POWER CALCULATIONS

11. REFERENCES

1. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version

5.0 [Internet]. U.S. Department of Health and Human Services: National Institutes of Health;

2017 Nov 27. Available from:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.p

12.2 Appendix B: List of Proposed Tables

Summary of Subject Disposition – All Subjects

Summary of Protocol Deviations – Safety Set

Summary of Demographics – Safety Set

Summary of Medical History by System Organ Class and Preferred Term – Safety Set

Summary of Prior and Concomitant Medications – Safety Set

Summary of Non-drug Therapies by System Organ Class and Preferred Term – Safety Set

Summary of Biomarkers: Change from Baseline – Safety Set

Summary of Biomarkers: Percent Change from Baseline – Safety Set

Summary of Exposure – Safety Set

Overall Summary of Treatment-emergent Adverse Events – Safety Set

Treatment-emergent Adverse Events by System Organ Class and Preferred Term – Safety Set

Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Highest Severity – Safety Set

Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Strongest Relationship to Study Drug – Safety Set

Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term – Safety Set

Treatment-emergent Adverse Events Leading to Study Withdrawal by System Organ Class and Preferred Term – Safety Set

Summary of Blood Chemistry Results – Safety Set

Summary of Hematology Results – Safety Set

Summary of Urinalysis Results – Safety Set

Summary of Vital Signs – Safety Set

Summary of ECG – Safety Set