A BETTER APPROACH TO DRUG DEVELOPMENT FOR LIVER DISEASES

JANUARY 2021 | INVESTOR PRESENTATION

smart drug
smart technology
smart development
FORWARD-LOOKING STATEMENTS

This presentation may contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. Such forward-looking statements are characterized by future or conditional verbs such as “may,” “will,” “expect,” “intend,” “anticipate,” “believe,” “estimate” and “continue” or similar words. You should read statements that contain these words carefully because they discuss future expectations and plans, which contain projections of future results of operations or financial condition or state other forward-looking information. Such statements are only predictions and our actual results may differ materially from those anticipated in these forward-looking statements.

We believe that it is important to communicate future expectations to investors. However, there may be events in the future that we are not able to accurately predict or control. Factors that may cause such differences include, but are not limited to, those discussed under Risk Factors in our periodic reports filed with the Securities and Exchange Commission, including the uncertainties associated with product development, the risk that products that appeared promising in early clinical trials do not demonstrate safety and efficacy in larger-scale clinical trials, the risk that we will not obtain approval to market our products, risks associated with delays, increased costs and funding shortages caused by the COVID-19 pandemic; the risks associated with dependence upon key personnel and the need for additional financing. We do not assume any obligation to update forward-looking statements as circumstances change.

This presentation does not constitute an offer or invitation for the sale or purchase of securities or to engage in any other transaction with Hepion Pharmaceuticals or its affiliates. The information in this presentation is not targeted at the residents of any particular country or jurisdiction and is not intended for distribution to, or use by, any person in any jurisdiction or country where such distribution or use would be contrary to local law or regulation.
NASH is a Healthcare Crisis

**NAFLD**
- non-alcoholic fatty liver disease
  - “Fatty liver” disease associated with obesity, diabetes, hypertension, etc.
  - Approx. 25% of global population (up to 100 million in U.S.)

**NASH**
- non-alcoholic steatohepatitis
  - A more severe form of NAFLD, with inflammation and liver scarring (fibrosis)
  - 1.5 – 6.5% globally (up to 17 million in U.S.)
THE CHALLENGES OF NASH DRUG DEVELOPMENT

Regulatory agencies require regression of several indices of liver disease by histological analysis:

- Fatty deposits, cell death, inflammation and/or liver scarring (fibrosis)

Most study outcomes have been disappointing:

- High placebo responses
- Low responses from most candidate drugs
- Several drug candidates discontinued

New approaches to developing NASH therapeutics are needed
HEPION’S APPROACH

SMART STRATEGY #1

Target Multiple Disease Processes With a Single Agent

- Visceral ectopic fat, adipose tissue inflammation and type 2 diabetes
- LCFAs, hyperinsulinaemia
- Adipocytokinesis
- Inflammation/fibrosis, cirrhosis and HCC

- Toxic lipids
- Cell death
- Inflammation
- Fibrosis
- Liver cancer

NAFLD: A multi system disease by Pablo Echeverria
HEPION’S APPROACH

SMART STRATEGY #2

Attenuate Disease Drivers

Most NASH drug candidates are agonists that amplify homeostatic processes to help regress disease. PPAR agonists, FGF agonists, FXR agonists, GLP-1 agonists, and THRβ agonists.

Cyclophilin inhibitors reduce harmful processes that drive disease progression.
HEPION’S APPROACH

SMART STRATEGY #3

State-of-the-art Bioinformatics and Artificial Intelligence

AI-POWR™

- Understand disease mechanisms
- Identify biomarkers
- Track disease progression and regression
- Predict drug responders
- Precision medicine
<table>
<thead>
<tr>
<th>Program</th>
<th>Pre-Clinical</th>
<th>Phase 1*</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>NDA Submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASH</td>
<td>IND 142904</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COVID-19</td>
<td>IND 151344</td>
<td></td>
<td></td>
<td>Will proceed if externally funded</td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>IND 1376787</td>
<td></td>
<td></td>
<td>Open to partnerships</td>
<td></td>
</tr>
</tbody>
</table>

*Separate Phase 1 programs were not conducted for each separate indication. The Phase 1 program was comprised of Single and Multiple Ascending Doses, and a Drug-Drug Interaction study.
### Theory

- **Cyclosporine A**
  - Nearly 40 years of clinical use as immunosuppressive drug for organ transplantation and autoimmune diseases

- **Voclosporin**
  - Aurinia Pharma

- **CRV431**

### Prediction and Experimentation

- **Cyclosporine A**
  - Modifications increase affinity for calcineurin and increase immunosuppression potency

- **Voclosporin**
  - Modifications increase affinity for calcineurin and increase immunosuppression potency (voclosporin)

- **CRV431**
  - Modifications increase affinity for cyclophilins (13-fold) and eliminate immunosuppression

### Findings

- Inhibition of each cyclophilin isoform produces distinct therapeutic effects

### Why Target Cyclophilins?

Cyclophilins shown to play deleterious roles in:
- Viral Hepatitis
- Cancers
- Acute And Chronic Lung Injury
- Myocardial Infarction
- Stroke
- Arthritis
- Atherosclerosis
- Thrombosis
- Aortic Aneurysm
- Coronary Artery Disease
- Pulmonary Arterial Hypertension
- ALS
- Alzheimers Disease
- Multiple Sclerosis
- Muscular Dystrophies
- Traumatic CNS Injury

---

**HEPION PHARMACEUTICALS**

**CRV431**

---

**HEPION PHARMACEUTICALS**

**CRV431**

---
MULTIPLE THERAPEUTIC ACTIONS THROUGH CYCLOPHILIN INHIBITION

**CRV431**
Pan-Cyclophilin Inhibitor
(Ki ≈ 1 nM)

**Cyclophilin A**
(cytosol and secreted)
Secreted from injured cells and acts as proinflammatory cytokine by binding to CD147

**Cyclophilin B**
(endoplasmic reticulum)
Promotes fibrotic scarring by controlling collagen production

**Cyclophilin D**
(mitochondria)
Regulates mitochondrial metabolism
Promotes mitochondrial pore opening leading to mitochondrial and necrotic cell death

CD17 pro-inflammatory receptors

- INFLAMMATION
- FIBROTIC SCARRING
- NECROTIC CELL DEATH
## ANTIFIBROTIC AND OTHER PRECLINICAL ACTIVITIES

### Human Cell Cultures

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>CRV431 Effects</th>
</tr>
</thead>
</table>
| Hepatic stellate cells, fibroblasts (multiple organs) | ▼ fibrotic gene expression  
| Blood platelets | ▼ procollagen and fibronectin secretion  
| | ▼ procoagulant platelet formation |

### Human Tissue Explants (Precision Cut Slice Cultures)

<table>
<thead>
<tr>
<th>Explants</th>
<th>CRV431 Effects</th>
</tr>
</thead>
</table>
| Liver explants (4 donors) | ▼ inflammatory/fibrotic gene expression  
| IPF lung explants (1 donor) | ▼ inflammatory/fibrotic protein secretion  
| | ▼ tissue fibrosis |

### Animal Models

<table>
<thead>
<tr>
<th>Model</th>
<th>CRV431 Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice (NASH)</td>
<td>82%▼ fibrosis; ▼ weight gain</td>
</tr>
<tr>
<td>Mice (liver fibrosis)</td>
<td>44%▼ fibrosis</td>
</tr>
<tr>
<td>Mice (kidney fibrosis)</td>
<td>42%▼ fibrosis</td>
</tr>
<tr>
<td>Rats (liver fibrosis)</td>
<td>48%▼ fibrosis; prevented cirrhosis</td>
</tr>
<tr>
<td>Mice (acute lung injury)</td>
<td>▼ BAL fluid inflammatory cytokines, neutrophils</td>
</tr>
<tr>
<td>Mice (diabetes)</td>
<td>▼ adiposity; ▼ weight gain</td>
</tr>
</tbody>
</table>
IN-HOUSE
ARTIFICIAL INTELLIGENCE
PROGRAM

- Multi-omics analyses – 25,000 data points per patient
- Identify biomarkers that predict response to CRV431
- Optimize and de-risk clinical trials through patient matching to CRV431 – precision medicine
Gene Expression Analysis
NASH is heterogenous disease, underpinned by complex biochemical and pathological processes.

Cluster By Response
- Learn response rates for treatment and placebo
- Identify patterns predicting response
- Select patients (trial enrichment)

AI: Trained Neural Nets
- Clinical Outcomes
- Biomarkers/Patients
- Optimize & Test
NASH CLINICAL PROGRAM

- **Phase 1** completed

- **Phase 2a** ongoing – completion Q2 2021

- **Phase 2b** in planning – starting Q3 2021
PHASE 1
HEALTHY SUBJECTS - SAFETY, TOLERABILITY AND PK

Single Ascending Dose (SAD)  
✓ N = 32  (24 CRV431; 8 Placebo)  
✓ Doses: 75 mg, 225 mg, 375 mg, 525 mg (single doses)  
✓ Drug Exposure is in the range in which efficacy was demonstrated in pre-clinical models  
✓ Pharmacokinetics are first order and support once daily dosing  
✓ No SAE’s, Mild AE’s, No dose response in AE’s or changes in clinical labs  
✓ No changes in vital signs or ECG  

Multiple Ascending Dose (MAD)  
✓ N = 25 (All CRV431)  
✓ Doses: 75 mg, 150 mg, 225 mg, 300 mg, 375 mg QD x 28 Days  
✓ Drug Exposure starting at 75 mg QD is in the range in which efficacy was demonstrated in pre-clinical models  
✓ Pharmacokinetics are first order and support once daily dosing  
✓ No SAE’s, Mild AE’s, No dose response in AE’s or changes in clinical labs  
✓ No changes in vital signs or ECG  
✓ Data supported initiation of Phase 2a NASH Trial  

Drug-Drug Interaction (DDI)  
✓ N = 18  
✓ Single CRV431 Drug Interaction Study with tenofovir
PHASE 2A
NASH SUBJECTS - SAFETY, TOLERABILITY AND PK

OBJECTIVES
- 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) patients compared to placebo control for 28 days
- Exploratory biomarkers of fibrosis and lipid metabolism: collagens, matrix metalloproteinases, lipidomics, and genomics
- Multi-omic/trait data analysis by AI-POWR™

STUDY DESIGN
- Multi-center (10 Sites), single-blind, placebo-controlled study
- Univariate Endpoints: AST, Pro-C3, ELF Score, Fibroscan

<table>
<thead>
<tr>
<th>Cohort*</th>
<th>Fibrosis Stage</th>
<th>N</th>
<th>Day 1 – 28, fasted oral dosing</th>
<th>Day 29 - 42</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>F2/F3</td>
<td>12</td>
<td>CRV431 75 mg</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td>6</td>
<td>Placebo</td>
<td>Observation/Follow-up</td>
</tr>
<tr>
<td>C</td>
<td>F2/F3</td>
<td>12</td>
<td>CRV431 225 mg</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td></td>
<td>6</td>
<td>Placebo</td>
<td></td>
</tr>
</tbody>
</table>

*randomized assignment; 2:1 – CRV431:placebo

Multivariate multi-omics-trait AI-POWR™ analysis to elucidate CRV431 activity biomarkers in F2/F3 NASH for Phase 2b Patient/Biomarker Selection
PHASE 2B
NASH SUBJECTS - EFFICACY

OBJECTIVES
- Efficacy of once daily (qd) 75 mg and 225 mg doses of CRV431 in biopsy proven NASH F2 and F3 patients compared to placebo over 6 months of dosing
- 1-point reduction in fibrosis score in liver biopsies (pathologist and AI read)
- AI-POWR™ identification of biomarkers of CRV431 response from multi-omics, clinical labs, and other trait data

STUDY DESIGN
- Multi-Center (28 US Sites), triple-blind, placebo-controlled (2:1), study
- Liver biopsies, MRE scans, Fibroscan, ALT, AST, Pro-C3, ELF-Score, fibrosis biomarkers, lipidomics, genomics, proteomics

<table>
<thead>
<tr>
<th>Cohort*</th>
<th>Fibrosis Stage</th>
<th>N</th>
<th>6 Months</th>
<th>3 Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>F2/F3</td>
<td>100</td>
<td>CRV431 75 mg</td>
<td>Observation/Follow-up</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td>50</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>F2/F3</td>
<td>100</td>
<td>CRV431 225 mg</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td></td>
<td>50</td>
<td>Placebo</td>
<td></td>
</tr>
</tbody>
</table>

*randomized assignment; 2:1 – CRV431:placebo

Multivariate multi-omics-trait AI-POWR™ analysis to update CRV431 activity biomarkers in F2/F3 NASH for Phase 3 Patient/Biomarker Selection
2021 ANTICIPATED EVENTS

CRV431

- Complete Ongoing Phase 2a NASH program by Q1-Q2, 2021
- Complete long-term animal toxicology (Q2, 2021)
- Continue to optimize and scale-up chemistry and manufacturing
- Complete additional clinical Drug-Drug Interaction study (Q2, 2021)
- Prepare for NASH Phase 2b (to start mid-2021) using AI-POWR™ strategies

AI-POWR™

- Continue to refine and extend AI-POWR™ for NASH and possible other indications
- Continue to develop IP for additional indications and business development strategies
HIGHLIGHTS
STATUS, EXPERIENCE, RESOURCES

- Oral, once-daily, multi-modal drug candidate – CRV431
- Clinical Phase 2a NASH trial in progress
- Clinical Phase 2b NASH trial planned for Q2/3 2021 start
- Strong safety/tolerability profile in preclinical and Phase 1
- Anti-fibrotic, anti-inflammatory, cytoprotective, anti-viral, anti-cancer, and metabolic regulation - all by cyclophilin inhibition (MOA)
- Artificial Intelligence Platform (AI-POWR™)
- ~30 years experience in cyclophilin inhibitor development
- Core team discovered and developed voclosporin for transplantation and autoimmune disease (FDA approved Jan 2021)
- Robust IP (including US, Europe, Australia, Canada, China, Japan, Korea)
Robert T. Foster, PharmD, Ph.D.
Chief Executive Officer

Hepion Pharmaceuticals Inc.
399 Thornall Street, First Floor
Edison, New Jersey, USA, 08837
Email: r foster@hepionpharma.com

www.hepionpharma.com