COCRYSTAL PHARMA, INC.

# Antiviral Therapies

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Chairman of the Board

# Forward Looking Statements

This presentation contains forward-looking statements, including the timing of our drug development programs. Risks include, but are not limited to, delays in manufacturing created by third parties and the ability of clinical research organizations to recruit patients. Forward-looking statements also are prefaced by words such as "expect," "plan," "intend," "anticipate," and similar words. Forward-looking statements are based on our current expectations and assumptions regarding our business, the economy and other future conditions. Because forward-looking statements relate to the future, they are subject to inherent uncertainties, risks and changes in circumstances that are difficult to predict. Our actual results may differ materially from those contemplated by the forward-looking statements for a variety of reasons, including the risk factors contained in our Form 10-K, as amended, for the year ended December 31, 2015, and our Form 10-Q for the quarter ending September 30, 2016. We caution you, therefore, against relying on any of these forward-looking statements. They are neither statements of historical fact nor guarantees or assurances of future performance. Except as required by applicable securities laws, we do not undertake any duty to update these forward-looking statements.

# Opportunities

*Significant unmet medical needs across a variety of viral infections*

| Influenza A & B | Hepatitis B & C | Norovirus |
|---|---|---|
| Seasonal and pandemic | Leading causes of liver failure and liver cancer | • Chronic (potentially orphan indication)<br>• Acute gastroenteritis |
| 3 - 5 million infections/year | Chronic infections<br>➢ 71 million HCV<br>➢ > 400 million HBV | > 250 million acute cases/year |
| Estimated economic impact of seasonal flu in US: $50B to $150B | Opportunity for shorter duration in HCV and a cure in HBV | No treatment available<br>Economic cost in the US alone > $5 Billion |

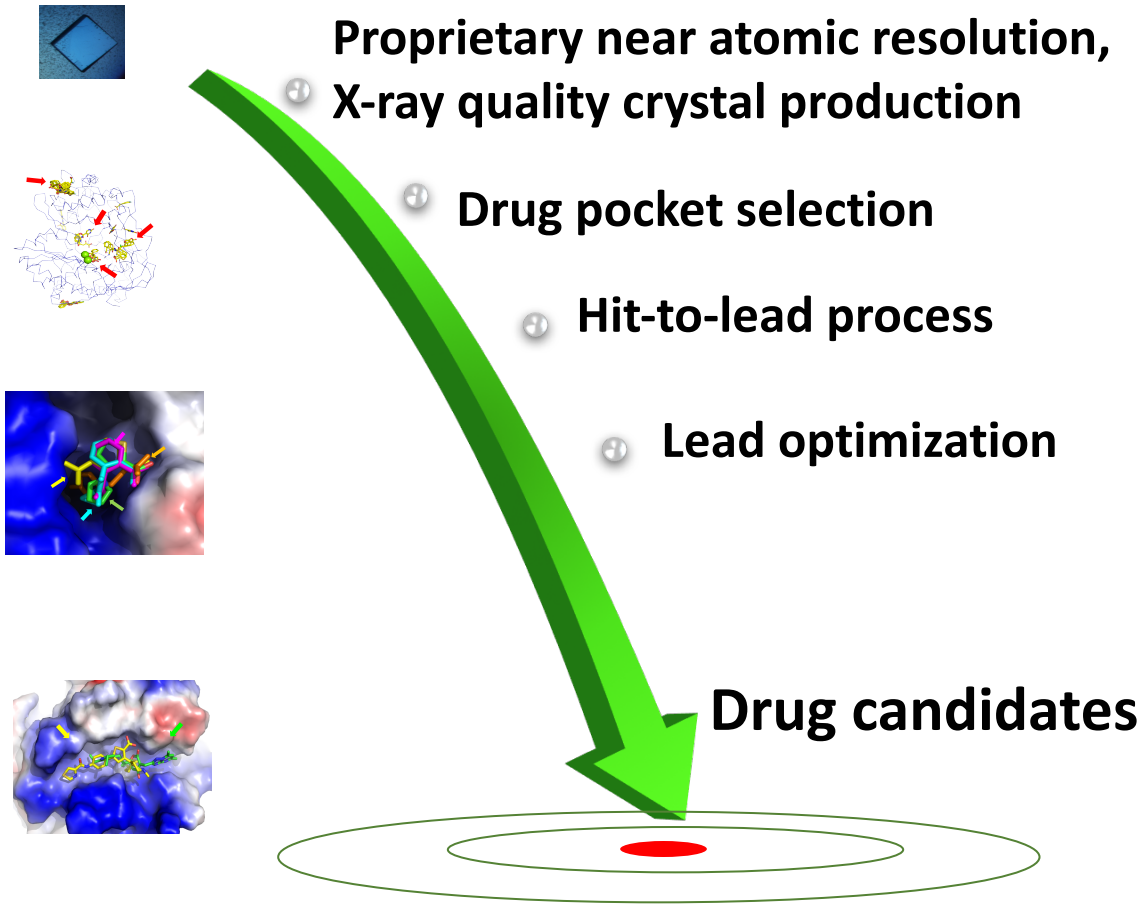
Reference: https://www.cdc.gov/flu, www.cdc.gov/hepatitis, www.cdc.gov/norovirus

# Company Highlights

- **Clinical stage antiviral company**
- **Multiple opportunities in different viral diseases**

| | |
|---|---|
| **Influenza** | **PB-2 inhibitors, PA inhibitors, PB-1 inhibitors** |
| **Hepatitis C** | **Non-nucleoside inhibitors, nucleoside inhibitors, NS5A inhibitors and helicase inhibitors,** |
| **Norovirus** | **Nucleoside inhibitors, non-nucleoside inhibitors** |
| **Hepatitis B (HBV) & Human Papilloma virus (HPV)** | **CRISPR-Cas 9 (gene editing)** |

# **Structure-Based Drug Design & Discovery Process:** Investing on Attractive Drug Binding Pockets

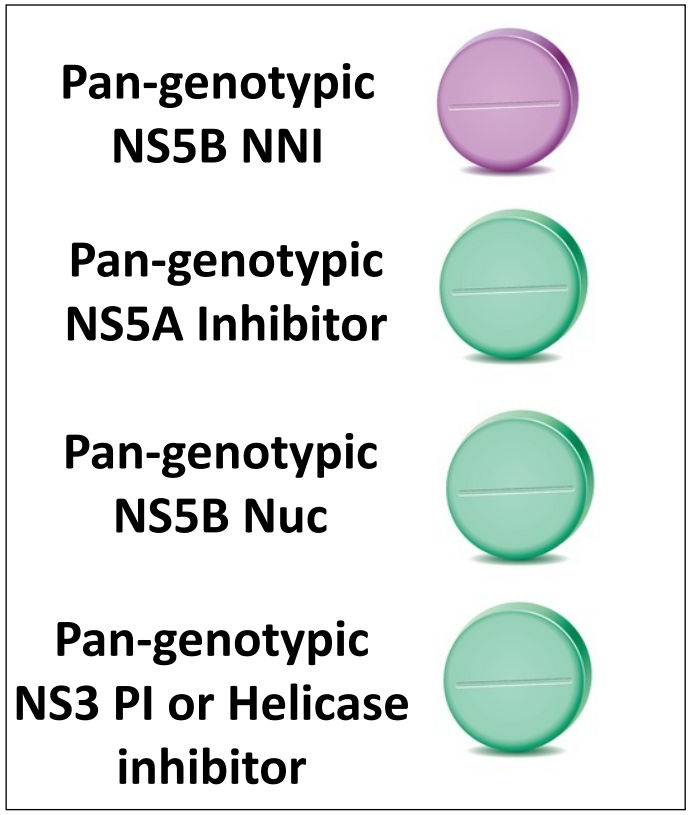


# Next Wave CC-31244 Combination Therapy with Existing HCV DAAs

- Potential **best-in-class HCV NNI** with a strong profile
  - Pan-genotypic, potent **low nM** NS5B polymerase inhibitor
  - Developed by Cocrystal's proprietary structure-based discovery platform
  - High barrier to drug resistance
  - Effective against known NNI drug resistant variants
  - Liver targeting
- Acceptable safety and efficacy profiles in Phase I studies
- Potential for an ultra-short therapy with existing HCV DAAs
- Phase 2a ready and open for collaboration

# HCV DAA Combinations

Multiple shots on goal in developing ultra-short, all oral pan-genotypic combination cure with/without partners




**Oral,**
**Pan-genotypic,**
**Ultra-short therapy**

# CC-31244 Phase Ia Clinical Trial Update

- A single- and multiple-dose assessment of the safety and pharmacokinetics of pan-genotypic NNI, CC-31244
  - Single-dose completed: five cohorts of healthy volunteers at 10, 50, 100, 200, and 400 mg
  - Multiple-dose completed: two cohorts of healthy volunteers at 200 mg x 7 days and 400 mg x 7 days)
  - Placebo or CC-31244 were well tolerated across all dose groups
  - No serious adverse events observed; no treatment discontinuations occurred

# CC-31244 Phase Ib Clinical Trial Update

- Proof-of-concept Phase 1b study near completion
  - HCV infected subjects with minimal fibrosis and no significant co-morbidities
  - Repeat-dose, randomized, monotherapy trial
  - Substantial and durable antiviral effect with an average **3 log** orders by 48 hours after dosing
  - Strong post-treatment antibiotic effect and no viral breakthrough observed

# CC-31244: Pan-genotypic NS5B NNI

- **CC-31244 HCV replicon $EC_{50}$ fold change, <6 fold**

HCV replicon/chimeric replicon $EC_{50}$ results

| Genotype | CDI-31244 $EC_{50}$, µM | $EC_{50}$ Fold change | Sofosbuvir $EC_{50}$, µM | $EC_{50}$ fold change |
|---|---|---|---|---|
| 1b | 0.005 | 1.0 | 0.042 | 1.0 |
| 1a | 0.009 | 1.8 | 0.034 | 0.8 |
| 2b | 0.026 | 5.2 | 0.028 | 0.66 |
| 3a | 0.011 | 2.2 | 0.14 | 3.2 |
| 4a | 0.021 | 4.2 | 0.047 | 1.1 |
| 5a | 0.002 | 0.4 | 0.075 | 1.7 |

# Phase 1a Study Design: Healthy Volunteers

**Single ascending doses (complete)** →

| 20 mg | 50 mg | 100 mg | 200 mg* | 400 mg |
|---|---|---|---|---|

N = 40; 30 CC-31244, 10 placebo;
* food effect assessed

**Multiple ascending doses (complete)** →

| 200 mg BID | 400 mg QD |
|---|---|

N = 16; 12 CC-31244, 4 placebo x 7 days

Endpoints

- Safety: adverse events (AEs) and laboratory abnormalities

# Phase 1b Study Design: HCV GT1 Patients

**HCV GT1**
**HCV RNA≥ 5 $log_{10}$IU/ml**
**Naive**

**Single doses**
**QD or BID x 7 days**

| 200 mg BID x 7 days | Status |
|---|---|
| N = 4; 3 CC-31244,1 placebo | Complete |

| 400 mg QD x 7 days | Status |
|---|---|
| N = 5; 4 CC-31244, 1 placebo | Complete |

| 600 mg QD x 7 days | Status |
|---|---|
| N = 5; 4 CC-31244, 1 placebo | Ongoing |

Endpoints

- Efficacy: changes in HCV RNA viral load
- Safety: adverse events (AEs) and laboratory abnormalities

# Study Results: Summary of Adverse Events (AEs)

## Healthy volunteers

- No serious AEs reported; no discontinuation due to AEs
- AE incidence rate: SAD = 23% (NNI), 50% (placebo); MAD = 25% (both)
- AEs with frequency > 1 in subjects receiving CC-31244
  - SAD: headache, 2/30 (6%); MAD: metallic taste, 2/12 (16%)

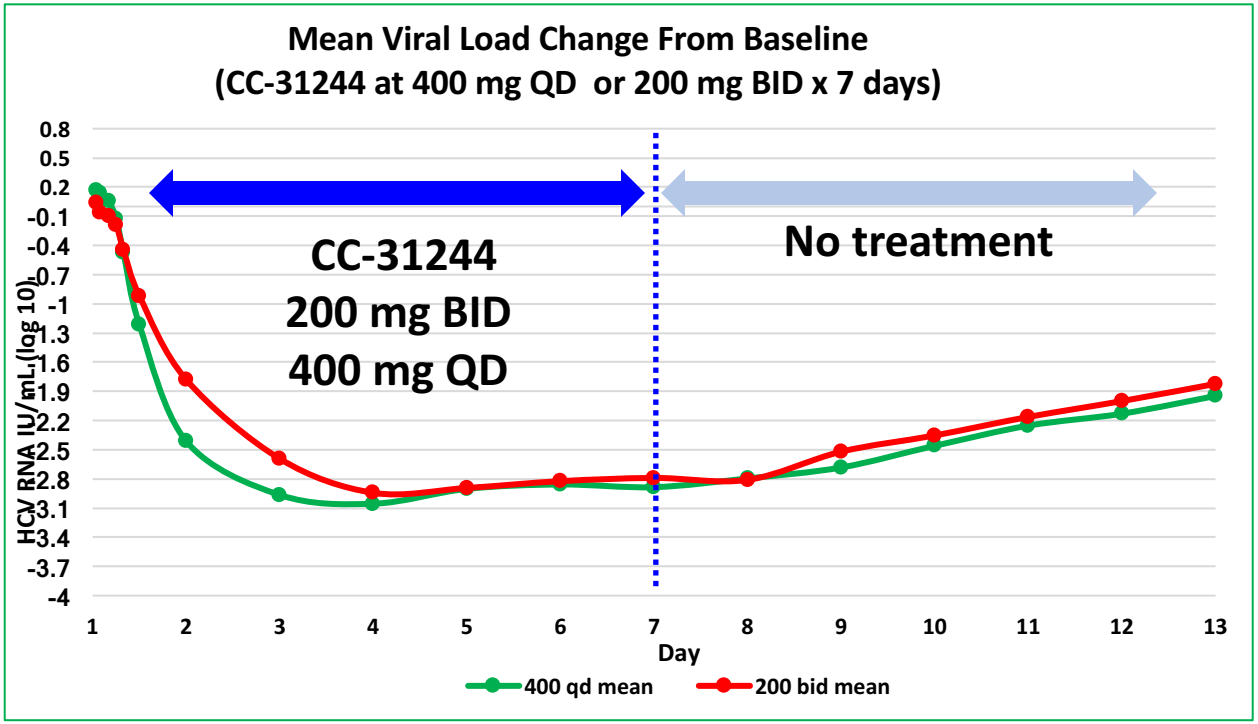
SAD = single ascending dose (20, 50, 100, 200, and 400 mg x 1 day)
MAD = multiple ascending dose (200 and 400 mg x 7 days)

## HCV GT1 patients

- No serious AEs reported; no discontinuation due to AEs
- AE incidence rate: 57% (NNI), 100% (placebo)
- No AEs with frequency > 1 in HCV GT1 patients receiving CC-31244

# Successful Viral Reduction in HCV GT1 Patients with HCV NNI, CC-31244

- HCV RNA viral load decline of **3 logs** by 48 hours
- After the NNI treatment, the viral load levels were slowly increased
- Drug resistance analysis ongoing



# HCV NNIs: Viral Load Comparison: CC-31244 is Best in class NNI

| Drug | Genotype | Dose (mg) | Treatment Duration (days) | Viral load reduction ($Log_{10}$IU/ml) |
|---|---|---|---|---|
| **CC-31244** ← | **Genotype 1-6** ← | **400** | **7 (QD)** | **-3.0** ← |
| **ABT-333* (Dasabuvir)** | Genotype 1 | 400 | 3 (BID) | -1.08 |
| | | 800 | 3 (BID) | -0.95 |
| **GS-9190 (Tegobuvir)** | Genotype 1 | 40 | 3 (BID) | -1.0 |
| | | 120 | 3 (BID) | -1.5 |

* FDA approved DAA

# Summary and Conclusion

- Showed an acceptable safety profile in both healthy volunteers and GT1 patients up to 400 mg x 7 days
- No serious adverse events or discontinuations due to adverse events
- Demonstrated HCV RNA viral load reduction of ~ 3 logs by 48 hrs
- Demonstrated a sustained post-treatment antiviral effect after the 7-day treatment
- Potential to be an important DAA in shorter HCV combination regimens

# Great Opportunity in Influenza Antiviral Market

- Seasonal and pandemic infection
  - 3-5 million cases of severe illness per year
  - 250,000 – 500,000 deaths worldwide
- Total estimated economic impact of seasonal flu in US: $87 billion
- Approved influenza therapies have limitations

Reference: https://www.cdc.gov/flu/about/disease/burden

# Influenza: Still Significant Unmet Need

- Approved influenza antivirals administered early, within 48 hours of onset of Flu symptoms

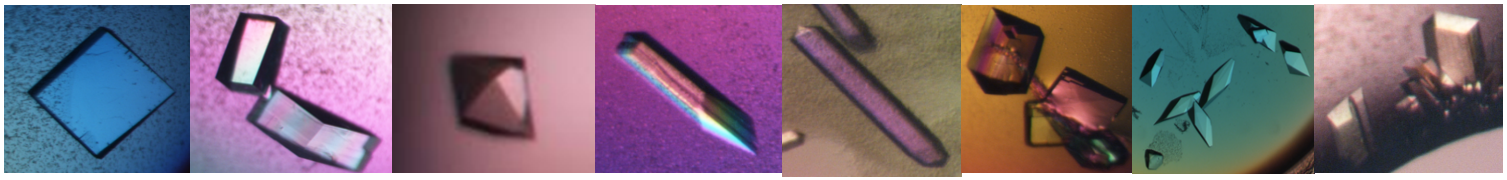
| Antiviral | Developer | MOA/Dosing |
|---|---|---|
| **Oseltamivir** (Tamiflu) | Gilead/ Genentech | Oral neuraminidase Inhibitor/75 mg bid for five days |
| **Zanamivir** (Relenza) | Biota/ GSK | Inhaled neuraminidase inhibitor/ 5 mg inhalation bid for five days |
| **Peramivir** (Rapivab) | Biocryst/ Shionogi | A single-dose intravenous neuraminidase inhibitor/600 mg IV |
| **Favipiravir** (Avigan, T-705) (Approved in Japan) | Toyama | Nuc, polymerase inhibitor/1,200 mg bid, followed by 600 mg bid for five days |

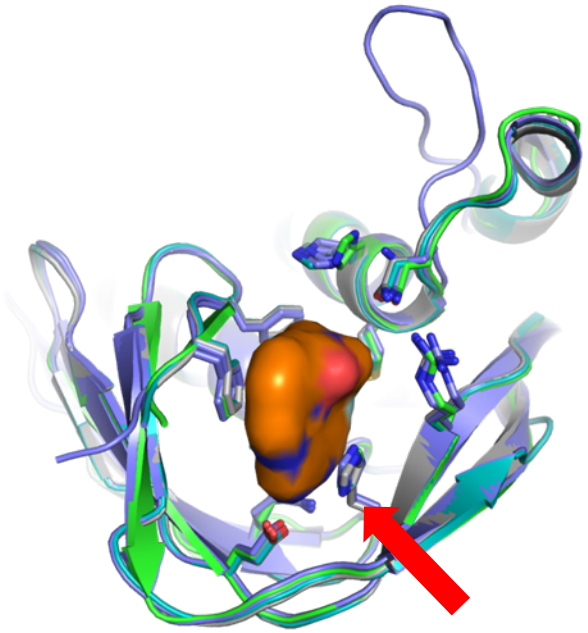
# Desirable Properties For Influenza Antivirals

- Superior pharmacological properties
  - Broad spectrum against pandemic and seasonal influenza strains
  - Efficacious against neuraminidase inhibitor (Tamiflu) resistant strains
  - Novel mechanism of action (prophylaxis and treatment)
- Flexible drug administration routes. i.e., oral, inhalation, and/or IV
- Satisfactory profile for safety and toxicity
- Excellent physicochemical properties

# Influenza A Preclinical PB-2 Lead Selected

**Influenza PB2 crystals**





**Influenza PB-2: PB-2 inhibitor**

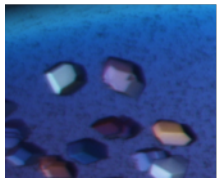
- CC-42344 selected as preclinical potent and selective lead (low nM inhibitor)
- Favorable PK profiles
- Excellent anti-influenza activity against pandemic, seasonal, and Tamiflu resistant influenza strains
- Binds a highly conserved PB-2 site
- Novel mechanism of action

# CC-42344 Exhibits Excellent Anti-influenza Activity for Influenza A Strains and Tamiflu Drug Resistant Strains

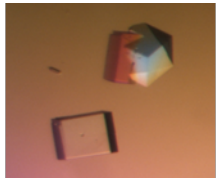
| Influenza serotype | Strain | CC-42344 EC50, nM |
|---|---|---|
| H1N1 | A/PR/8/34 | 1 |
| H1N1 | A1/Denver/1/57 | 3 |
| H1N1 | A/Fort Monmouth/1/47 | 2 |
| H1N1 | A/CA/27/07 | 1 |
| H1N1 | A/NY/18/09 | 5 |
| H3N2 | A/AICHI/2/68 | 0.2 |
| H1N1-Amantadine resistant | A/Virginia/01/2006 S31N | 9 |
| H1N1- Tamiflu resistant | A/HK/2369/09 H274Y | 9 |
| H3N2-Tamiflu resistant | A/Wuhan/395/95 | 0.5 |

# Early Stage Programs

- CRISPR-Cas9 program
  - In-licensed from Duke University and Emory University for treatment of HBV and HPV
  - POC animal model studies will be initiated
- Norovirus program (Cocrystal owns strong nuc IP)
  - Structure-based NNI discovery ongoing
  - NoV and Norwalk polymerase crystals developed
  - Additional NoV nucleoside lead discovery ongoing



Human Noro



Human Norwalk

Murine Noro

# Summary

- HCV NNI CC-31244 – Complete the ongoing Phase 1b study, and initiate Phase 2a ultrashort treatment (combination studies for 2-4 weeks) based on recent paper in *Lancet Gastro Hepatol* 1(2):97-104, 2016

- Influenza PB-2 CC-42344: Lead candidate selected (1 nM) and moving to initiate IND-enabling studies

- Continue Noro, and CRISPR-Cas9 (HepB and HPV) programs

- Open to partner(s) for our assets in strategic locations

# THANK YOU

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