Developing Future Antiviral Therapies
Forward Looking Statements

This presentation contains forward-looking statements, including the timing of our drug development programs. Risks include 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 those contained in our Form 10-K, as amended, for the year ended December 31, 2014. 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. We do not undertake any duty to update these forward-looking statements.
Company Highlights

**Leadership**
World renowned scientific and business leadership

**Therapeutic focus**
Creating new antiviral drug candidates in areas of high unmet medical needs (e.g. influenza, hepatitis, norovirus, etc.)

**Clinical**
Anticipate initial clinical filing in 2015 followed by human trials

**Technologies**
Innovative and proprietary drug design technologies for unmet medical needs
Cocrystal Today

*Developing the future of antiviral therapies*

- Influenza
- Norovirus
- Hepatitis
- Other Viruses

Structured-based drug design platform + nucleoside chemistry and biology
Scientific Leadership

Dr. Roger Kornberg  
Cocrystal Co-founder  
2006 Nobel prize winner in chemistry

Dr. Raymond Schinazi  
Cocrystal Co-founder  
Founder of Pharmasset, Idenix, Triangle
Cocrystal Pharma Evolution

Cocrystal Pharma
- High throughput cocrystal structure evaluation and structure-based drug design
- Nobel prize winning expertise
- HCV: pan-GT NNI & first-in-class helicase inhibitor
- Active discovery programs in other viruses including: influenza, dengue, noroviruses

Founded in 2007

RFS Pharma
- World class nucleoside discovery/development team
- HCV: Novel nucleosides (Nuc) and prodrugs
- HCV: NS5A and protease inhibitors
- Norovirus: nucleoside inhibitors

Founded in 2004

November, 2014 Merger
Opportunities

There exists significant unmet medical needs across a large variety of viral infections...

<table>
<thead>
<tr>
<th></th>
<th>HCV</th>
<th>Noro</th>
<th>Influenza A &amp; B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description</strong></td>
<td>Leading cause of liver failure and liver cancer</td>
<td>Chronic &amp; Acute gastroenteritis</td>
<td>Seasonal and pandemic</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td>80 - 170 million chronic infections</td>
<td>&gt;250 million acute cases/year</td>
<td>3 - 5 million chronic infections/year</td>
</tr>
<tr>
<td><strong>Opportunity</strong></td>
<td>Opportunity for shorter duration and improved accessibility</td>
<td>Economic cost in the US alone is &gt;$5 Billion</td>
<td>Estimated economic impact of seasonal flu in US: $50B to $150B</td>
</tr>
</tbody>
</table>
Structure-based Drug Discovery Technology

Example of HCV fragment hits

Inhibitor A  
Inhibitor B  
Inhibitor C

Advantages of the Cocrystal approach

- Provides 3D structure of inhibitor complexes at near-atomic resolution with immediate insight to guide SAR
- Identifies novel binding sites
- Allows rapid turnaround of structural information through highly automated X-ray data processing and refinement
Technology Platform Focuses on Viral Replication Drug Targets Through Cocrystalization

Building a foundation with high resolution X-ray data (<2Å)

>800 cocrystal structures
Avg resolution <2Å
2015 Pipeline

Viral Disease | Lead Discovery | Lead Optimization | Preclinical | IND | Phase I/II

Hepatitis C (3 near-clinical assets)
- CC-1845 (NS5B-Nuc)
- CC-2068 (NS5A)
- CC-31244 (NS5B-NNI)
- CC-31326 (Helicase)

Norovirus
- CC-1845 (Nuc)

Influenza
HCV Approach: Multiple shots on goal

De-risked near-term approach creating multiple “Shots on Goal”

- Pan-genotypic NS5B Nuc
- Pan-genotypic NS5A Inhibitor
- Pan-genotypic NS5B NNI
- Pan-genotypic Helicase Inhibitor

Multiple possibilities of an all oral HCV regimen
CC-1845: Compelling HCV Drug Candidate

*Nucleoside Prodrug: Potential backbone for next generation combination therapy*

- Pan-genotypic
- Delivers multiple active triphosphates
  - Two of the active metabolites show comparable potency to sofosbuvir
- Low cytotoxicity based on preliminary data
- Resistance selection was challenging
  - S282T selected only upon the 5th attempt
- Rapid liver delivery of parent nucleosides and the NTPs (PK studies)
- Synergistic/additive with a proprietary NS5A inhibitor (CC-2068) and NNI (CDI-31244)
- Anticipated QD dosing
CC-1845: Nucleoside Profile

- Potent
- High barrier to resistance
- No drug-drug interactions

- Cascade of rNTP metabolite generation
- Half-lives of rNTP will support once-a-day dosing

### Pan-genotypic activity

<table>
<thead>
<tr>
<th>HCV replicon (Huh-7): clinical isolates</th>
<th>EC$_{50}$ (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT 1a</td>
<td>0.70</td>
</tr>
<tr>
<td>GT 1b</td>
<td>0.88</td>
</tr>
<tr>
<td>GT 2a</td>
<td>0.19</td>
</tr>
<tr>
<td>GT 2b</td>
<td>0.21</td>
</tr>
<tr>
<td>GT 3a</td>
<td>0.17</td>
</tr>
<tr>
<td>GT 4a</td>
<td>0.38</td>
</tr>
</tbody>
</table>

### Preliminary cytotoxicity data

<table>
<thead>
<tr>
<th>Cells</th>
<th>CC$_{50}$ (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huh-7</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>Human PBM</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>Vero</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>CEM</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>Human bone marrow</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>Mitochondrial toxicity</td>
<td>&gt; 50</td>
</tr>
</tbody>
</table>
CC-1845: Favorable NTP Formation

CC-1845 and Sofosbuvir incubated with Primary Human Hepatocytes at 50 μM for 4 hours (n=3)

![Graph showing NTP formation with CC-1845 and Sofosbuvir](image-url)
CC-1845: Greater Levels of NTP \textit{in vivo}

Comparative single IP dosing study in mice with SOF at 10 mg/kg in the liver

 Liver AUC, ng.h/mL liver

- **CC-1845 NTP1**
  - NTP1: 181

- **CC-1845 NTP2**
  - NTP2: 25,400

- **CC-1845 NTP3**
  - NTP3: 13,100

- **Sofosbuvir NTP**
  - SOF-NTP: 11,700
CC-1845: Interspecies Hepatocytes

CC-1845 and sofosbuvir comparative study in five species: 50 μM at 4 h
CC-1845: Comparable Potency

2 of the 3 metabolites of CC-1845 showed comparable potency to sofosbuvir against the HCV viral polymerase

<table>
<thead>
<tr>
<th>NS5B enzyme</th>
<th>IC$_{50}$ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NTP1</td>
</tr>
<tr>
<td>GT 1b WT</td>
<td>&gt; 200</td>
</tr>
</tbody>
</table>
CC-1845: HCV Nuc Chain Terminator

CC-1845 terminates HCV RNA replication: X-ray data confirms highly efficient mechanism of action

Cocrystal’s high resolution X-ray structure
# CC-1845: IND Candidate Properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Value/Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pan-genotypic</strong></td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td>GT1b EC$_{50}$, µM</td>
<td>1.1 ± 0.7 µM</td>
</tr>
<tr>
<td>Liver targeting</td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td>Cytotoxicity [includes human cardiomyocytes, Mitotox (galactose vs glucose) &amp; bone marrow toxicity]</td>
<td>Early data shows minimal cytotoxicity at clinically relevant conc. in over 22 human/mammalian cell types (proliferating and non-proliferating); no evidence of <em>in vitro</em> mitochondrial toxicity, cardiomyocyte or bone marrow toxicity</td>
</tr>
</tbody>
</table>
| 1. Selectivity vs. Human DNA pol alpha, beta, gamma | 1. > 100 µM for all three NTPs and across all 3 Pols  
2. Selectivity vs. Human RNA pol II  
3. Human mitochondrial RNA pol (POLRMT) |
| 1. Human CYP2B6, 2C8, 2C9, 2C19, 3A (direct)   | 1. Low risk of drug-drug interaction thru direct or time-dependent CYP inhibition.  
2. No significant inhibition across 8 human transporters |
| 2. Human Transporters: OCT2, ASBT, BCRP, NTCP, OAT1, OAT3, OATP1B1, OATP1B3 | GLP hERG assay  
IC$_{50}$ > 30 µM (25% inhibition at 30 µM) |
| CV/respiratory in dogs (GLP): tested 60, 200, 600 mg/kg single dose | Respiratory parameters were unaffected. Minor fluctuations in blood pressure/heart rate and QT/QTc at 600 mpk, were of minimal clinical significance. |
| Genotoxicity (AMES, chromosome aberration)     | Negative in both assays                                                                                                                          |
| Stability in Human liver & human intestinal microsomes | $T_{1/2}$: 39.4 min (liver microsomes) & > 145 min in intestinal microsomes (low clearance in both microsomes) |
| *In vitro* combination study                  | Additive/synergistic with CC-31244 & CC-2068                                                                                                   |
CC-2068: Pan-genotypic NS5A

- Novel, highly potent, pan-genotypic, NS5A inhibitor (GT1b EC$_{50}$ < 10 pM)
- CC-2068 produces an active metabolite (also a pM HCV inhibitor)
- No cytotoxicity observed
- Favorable PK properties
- Favorable *in vitro* ADMET properties
- Potentially an excellent combination drug candidate with Nuc and/or NNI
- IND-enabling studies in progress
## CC-2068: IND Candidate Properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pan-genotypic</strong></td>
<td>Yes</td>
</tr>
<tr>
<td>GT1b EC$_{50}$</td>
<td>2.2 pM; also has a pM active metabolite</td>
</tr>
<tr>
<td>Liver targeting</td>
<td>Yes; 2 h dog liver study: 13.4-fold higher liver concentration than plasma &amp; exceeds EC$_{50}$</td>
</tr>
<tr>
<td>Stability in Human liver &amp; human intestinal microsomes</td>
<td>$T_{1/2}$: &gt; 145 min (in both liver &amp; intestinal microsomes) (low clearance in both microsomes)</td>
</tr>
<tr>
<td>Cytotoxicity</td>
<td>No</td>
</tr>
<tr>
<td>1. Human CYP2B6, 2C8, 2C9, 2C19, 3A (direct)</td>
<td>Large margins (&gt; 100-fold) between any inhibitory activity and efficacious concentrations; no risk for clinical drug-drug interaction</td>
</tr>
<tr>
<td>2. Human Transporters: OCT2, ASBT, BCRP, NTCP, OAT1, OAT3, OATP1B1, OATP1B3</td>
<td></td>
</tr>
<tr>
<td>hERG</td>
<td>No</td>
</tr>
<tr>
<td>Caco2 A-B (at 10 µM), $10^{-6}$ cm/s</td>
<td>&lt; 0.05 (low forward permeability)</td>
</tr>
<tr>
<td>Caco2 B-A (at 10 µM), $10^{-6}$ cm/s</td>
<td>&lt; 0.24 (no significant efflux)</td>
</tr>
<tr>
<td>Genotoxicity (AMES, chromosome aberration)</td>
<td>Negative in both assays</td>
</tr>
<tr>
<td>In vitro combination study</td>
<td>Additive/synergistic with CC-1845 &amp; CC-31244</td>
</tr>
</tbody>
</table>
CC-31244: Pan-genotypic NNI

- Highly potent NS5B polymerase inhibitor (EC$_{50}$ = 7 nM)
- Pan-genotypic activity against all genotypes (1-6)
- No off-target activities and favorable in vitro ADMET properties
- No cytotoxicity
- Excellent activity against common drug resistant variants (IC$_{50}$ fold change < 5-fold)
- Favorable PK properties
- Liver targeting
- IND-enabling studies in progress
CC-31244: Pan-genotypic NNI

*High barrier to drug resistance*

**Drug resistance variants**
- S365T (NNI-4)
- N316Y (NNI-4)
- L419M (NNI-2)
- S282T (Nuc)

**IC₅₀ fold increase**
- 31228
- 31244
- 959
- 985
- HCV-796 (Viropharma)

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**Notes:**
- Cocrystal’s NNI-4 Leads
- Cocrystal’s Backup Leads

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cocrystalpharma.com
CC-31244: Excellent Liver Targeting

Rat liver study

(n = 3/timepoint)

Avg: 27 µM
(x1,600 EC\(_{50}\))

Avg: 5.4 µM
(x320 EC\(_{50}\))

Avg: 0.12 µM
(x7.2 EC\(_{50}\))

<table>
<thead>
<tr>
<th>Time</th>
<th>Plasma</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 h</td>
<td>5000</td>
<td>2000</td>
</tr>
<tr>
<td>4 h</td>
<td>10000</td>
<td>500</td>
</tr>
<tr>
<td>24 h</td>
<td>15000</td>
<td>100</td>
</tr>
</tbody>
</table>
CC-31244: Structure-guided NNI

CC-31244 extends from NNI-4 to active site
## CC-31244: IND Candidate Properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan-genotypic</td>
<td>Yes</td>
</tr>
<tr>
<td>GT1b EC\textsubscript{50}</td>
<td>8.5 ± 1.0 nM</td>
</tr>
<tr>
<td>Liver targeting</td>
<td>Yes</td>
</tr>
<tr>
<td>Intrinsic clearance (liver microsomes)</td>
<td>Human Cl\textsubscript{int} = 131 µL/min/mg; Half-life 53 min</td>
</tr>
<tr>
<td>Cytotoxicity [includes Mitotox (galactose vs glucose: 3 days)]</td>
<td>No or little cytotoxicity observed in 13 human/mammalian cell types</td>
</tr>
<tr>
<td>1. Human CYP 2B6, 2C8, 2C9, 2C19, 3A (direct)</td>
<td>Large margins (&gt; 100-fold) between any inhibitory activity and efficacious concentrations; no risk for clinical drug-drug interaction</td>
</tr>
<tr>
<td>2. Human Transporters: OCT2, ASBT, BCRP, NTCP, OAT1, OAT3, OATP1B1, OATP1B3</td>
<td></td>
</tr>
<tr>
<td>Genotoxicity (AMES, chromosome aberration)</td>
<td>Negative in both assays</td>
</tr>
<tr>
<td>hERG</td>
<td>No inhibition</td>
</tr>
<tr>
<td>Caco2 A-B, 10\textsuperscript{-6} cm/s</td>
<td>7.1 (high forward permeability)</td>
</tr>
<tr>
<td>Caco2 B-A, 10\textsuperscript{-6} cm/s</td>
<td>44.4 (moderate efflux)</td>
</tr>
<tr>
<td>Safety (off-target) profile</td>
<td>Excellent</td>
</tr>
<tr>
<td>\textit{In vitro} combination study</td>
<td>Additive/synergistic with CC-1845 &amp; CC-2068</td>
</tr>
</tbody>
</table>
Additional Candidates Identified for HCV

- **Nucleoside**
  - Four unique nucleoside analogs identified
  - Potency in a genotype 1b replicon assay ranges from 200 to 600 nM
  - No toxicity (> 80 μM) was observed in PBM, CEM and Vero cells

- **NS5A**
  - Pre-clinical lead selected, CC-2069
  - Excellent *in vitro* profile

- **NNI**
  - Pre-clinical lead selected, CC-959
  - Excellent *in vitro* profile
HCV Helicase Program

*Provides unique opportunities for drug combinations*

- Creates a new option for HCV combination therapy
- First-in-class pan-genotypic inhibitors (new mechanism of action)
- Highly conserved drug binding mode demonstrated in all genotype crystals developed (1-6)
- Potentially an ideal combination candidate with HCV NS5B Nuc, NNI, NS5A, and/or protease inhibitors
- Inhibits essential viral RNA unwinding process
HCV Pan-genotypic NS3 Helicase Inhibitors

HCV genotype crystals (1-6) developed

GT1b  GT1a  GT1b FL  GT2a  GT3a  GT4a  GT5a  GT6a
Pan-genotypic binding mode of HCV helicase inhibitor

Genotype 1-6 overlay cocrystal structures
Norovirus Program

*Norovirus polymerase leads: nucleoside inhibitor and NNI*

- Novel anti-norovirus Nuc prodrug (CC-1845) developed: confirmed activity based on Norwalk replicon and enzyme assay; also active against HCV
- Favorable PK properties demonstrated
- Drug resistance evaluation for Norovirus (in progress)
- Structure-based NNI lead discovery (in progress)
- Expect to be used as prophylaxis and for acute and chronic norovirus infections; especially in immunocompromised patients
Influenza Program

*Influenza leads: PB2, PB1 and PA Inhibitors*

- Focus on three different classes of influenza polymerase inhibitors: PB2 (cap-binding), PB1 (polymerase), and PA (endonuclease)
- Expect to complete PB2 lead optimization by Q4
- IND-enabling study of PB2 inhibitor scheduled for 2016
2015 Goals

*Accelerate transition into a clinical biopharmaceutical company*

- **Development**
  - Progress regulatory filings as soon as possible
  - CC-1845 is first priority, followed closely by CC-31244 and CC-2068

- **Research**
  - Select lead drug candidate for Influenza
  - Progress norovirus program for both nucleoside and NNI compounds

- **Operations**
  - Continue transition to a fully-listed, Nasdaq Company
  - Enhance leadership team and technical capabilities
Looking Forward to 2016

*Potentially transformational year*

- **HCV**
  - Advance multiple pan-genotypic DAA’s into Phase 1
  - Potential unique combination regimen (Nuc+NS5A+NNI)

- **Norovirus**
  - Initiate clinical program against norovirus
  - Advance additional DAAs

- **Influenza**
  - Potentially initiate IND-enabling studies for PB-2 inhibitors
  - Develop PB-1, PA leads
Leadership

Board of Directors and Key Management

Raymond Schinazi (Chairman)

Phil Frost

David Block

Jane Hsaio

Steven Rubin

Gary Wilcox

Jeffrey Meckler

Sam Lee
Developing Future Antiviral Therapies