CRN04777: PHASE 1 MULTIPLE ASCENDING DOSE (MAD) PRELIMINARY RESULTS

March 30, 2022
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This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions, and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.
CRN04777 MAD Results Build on Pharmacologic Proof-of-Concept Data from SAD Study

Well-tolerated at doses from 30 mg to 120 mg administered once daily for 10 days
  • No Serious Adverse Events (SAEs)
  • All Adverse Events (AEs) considered mild/moderate

Further demonstrated pharmacologic POC by showing dose-dependent:
  • Decreases in fasting insulin, leading to increases in fasting plasma glucose
  • Reversal of sulfonylurea-induced insulin secretion in a pharmacologic model of disease

Favorable pharmacokinetics results support once daily dosing
  • Showed oral bioavailability with ~40-hour half-life
  • PK results and exposures consistent with expectations from SAD data

Next steps: Meet with regulators to discuss design of clinical program in patients

MAD: Multiple-ascending dose SAD: Single-ascending dose; POC: Proof-of-concept; PK: Pharmacokinetic
Preclinical POC
Δ Glucose & Hormones, PK, Safety

Phase 1 Healthy Volunteers

Phase 1 Healthy Volunteer Safety, Pharmacologic POC
Δ Glucose & Hormones, PK, Safety

Phase 2/3 Trials (Patients)

Phase 2/3 Safety, Disease Efficacy
Δ Glucose & Hormones, PROs, PK, Safety

POC: Proof-of-concept; PK: Pharmacokinetic; PRO: Patient reported outcome
Congenital Hyperinsulinism (HI) Results in Life Threatening Recurrent Hypoglycemia

Congenital HI patients secrete insulin even when blood sugar is low, causing hypoglycemia

**Congenital HI is a devastating rare disease (U.S. prevalence = 1.5-2K)**

- Untreated hypoglycemia can result in life-threatening acute complications and long-term neurodevelopment disorders
- Early identification and continuous intensive glucose management are critical
- Current treatment paradigms place high burden of care on families with all too frequent suboptimal outcomes
- Six Global Centers of Excellence named for treatment of patients with HI
- Robust global patient advocacy such as Congenital Hyperinsulinism International (www.congenitalhi.org)
Unmet Medical Needs in Congenital HI are Very High

Patient & Parent Goals

✓ Avoid hypoglycemia and its consequences including neurological damage
✓ Safely sleep through the night
✓ Avoid pancreatectomy
✓ Eliminate feeding tubes
✓ Reduce injections and glucose sticks
✓ Avoid side effects of diazoxide and other treatments
✓ Medical management until HI resolves with age
✓ Be a kid not a patient

From Congenital Hyperinsulinism International’s 2022 Rare Disease Day Awareness Campaign
Current Congenital HI Therapies have Limited Efficacy and Additional Shortcomings

Direct Glucose Support

In use:
- Intravenous glucose sometimes requiring central venous administration
- Enteral dextrose delivered via a gastrostomy or nasogastric tube

Shortcomings include:
- Prolonged hospitalization
- Burdensome delivery route
- May contribute to feeding issues including eating aversion
Current Congenital HI Therapies have Limited Efficacy and Additional Shortcomings

Shortcomings related to safety, efficacy, & route of administration hamper congenital HI treatments

Direct therapies

- IV glucose
- Enteral dextrose (GT/NG)

In use:
- Continuous IV glucagon infusion (for prevention)
- Injectable glucagon/analog boluses (for acute hypoglycemia)

In development:
- Glucagon & Analog (continuous subcutaneous infusions)

Liver Directed

In use:
- Ineffective in ~50% of patients; black box warning
- Injectable SST2 agonists (off-label)
- Pancreatectomy (complete or partial)

In development:
- Injected GLP-1 antagonist

Pancreas Directed to Suppress Insulin Secretion

In use:
- Diazoxide

Target Tissue Directed to Block Insulin Action

In development:
- Insulin Receptor Antibody (IV)
  - Requires biweekly IV administration

Liver

Glucagon (α-cells)

Glucose Release

High blood sugar

Insulin (β-cells)

Glucose Uptake

Tissues

Low blood sugar

Pancreas

Glucose
CRN04777: Oral SST5 Agonist with Potential to Overcome Shortcomings of Competing Therapies

We believe CRN04777 is the only investigational oral product candidate in clinical development that is designed for **ALL** hyperinsulinism patients.
Syndromic hyperinsulinisms (e.g., those associated with Beckwith-Wiedemann syndrome, Sotos syndrome, Kabuki syndrome, and Turner syndrome) may also respond to SST5 agonism.
CRN04777 MAD Study Designed to Build on SAD Pharmacologic Proof-of-Concept Data

Follows Crinetics’ core endocrine strategy of using hormonal biomarkers to drive development

**MAD Study Goals**

- Evaluate safety and tolerability with repeat dosing
- Evaluate PK at steady state
- Evaluate basal PD with repeat dosing
- Evaluate PD after a sulfonylurea challenge (pharmacologic model of disease)
- Inform dose selection for patient studies

**Pharmacodynamic Assessments**

1. Fasting plasma glucose and insulin
2. Sulfonylurea (SU) challenge

**Proof-of-Concept**

- Dose dependent suppression of SU-induced insulin secretion with CRN04777

MAD: Multiple-ascending dose; SAD: Single-ascending dose; Proof-of-concept; PK: Pharmacokinetics; PD: Pharmacodynamics
CRN04777 was Well Tolerated with No Dose Discontinuations due to Adverse Events

As expected, GI side effects (mild to moderate nausea, vomiting, diarrhea) were the most common treatment-related adverse events. The time course for these dose-dependent GI events shortly followed treatment initiation and resolved without the need to discontinue study drug. No study drug discontinuations due to Adverse Events. No Serious Adverse Events. No safety signals seen with vital signs, laboratory testing, ECGs.

<table>
<thead>
<tr>
<th>Most Frequent TEAEs</th>
<th>Placebo (SAD+MAD) (N=29) n (%)</th>
<th>'4777 (SAD+MAD) (N=78) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>0 (0)</td>
<td>15 (19.2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 (0)</td>
<td>7 (9.0)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0 (0)</td>
<td>5 (6.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>0 (0)</td>
<td>5 (6.4)</td>
</tr>
<tr>
<td>Chills</td>
<td>0 (0)</td>
<td>3 (3.8)</td>
</tr>
<tr>
<td>Hypoglycaemia*</td>
<td>0 (0)</td>
<td>3 (3.8)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0 (0)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0 (0)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Phlebitis</td>
<td>4 (13.8)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Skin Irritation</td>
<td>2 (6.9)</td>
<td>1 (1.3)</td>
</tr>
</tbody>
</table>

*Post glucose clamp and not treatment related

TEAE: Treatment emergent adverse event; GI: Gastrointestinal; SRL: Somatostatin receptor ligand; ECG: Electrocardiogram
MAD PK Results and Exposures were Consistent with Expectations from SAD Data at the Same Doses

Favorable PK results support once daily dosing

**Steady State PK**

- Oral bioavailability
- Favorable half-life of ~40 hours
- Rapidly absorbed with a $t_{\text{max}}$ of ~1-3 hours

**Concentration-Time Profile at Steady State (Day 9)**

Data represent mean ± SEM; MAD: Multiple-ascending dose; PK: Pharmacokinetic; SAD: Single-ascending dose; QD: Once daily

* n=1 subject withdrew consent (not treatment related)
Dose-Dependent Decrease in Fasting Insulin Led to Increases in Plasma Glucose

CRN04777 drove rapid and sustained changes in insulin and glucose levels in healthy volunteers.

Fasting Insulin Levels

Plasma Glucose Levels

Data represent mean ± SEM; PBO: Placebo; QD: Once daily

(a) Day 1 measurement occurs prior to the first dose of CRN04777. Measurements on Days 2-9 occurred after ≥ 10 hours overnight fasting and prior to CRN04777 daily dosing. Measurement on Day 10 was after sulfonylurea dose, hence excluded.

(b) n=1 subject withdrew consent (not treatment related)
CRN04777 MAD Study Designed to Build on SAD Pharmacologic Proof-of-Concept Data

Follows Crinetics’ core endocrine strategy of using hormonal biomarkers to drive development

**Sulfonylurea (SU) Challenge**

**Baseline (Day -2)**
- **SU (po)**
  - IV glucose
  - “Glucose Clamp” with continuously adjusted glucose infusion rate (GIR) while fasting
  - Multiple blood draws to measure glucose & insulin; Monitor GIR

**Treated (Day 10)**
- **4777 (po)**
  - IV glucose
  - “Glucose Clamp” with continuously adjusted glucose infusion rate (GIR) while fasting
  - Multiple blood draws to measure glucose & insulin; Monitor GIR

Healthy volunteers receive repeated oral doses of CRN04777 for 10 days and a sulfonylurea challenge on Day 10 (n = 9/cohort)

MAD: Multiple-ascending dose  SAD: Single-ascending dose; po: By mouth

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**Pancreas**

**Sulfonylureas block K<sub>ATP</sub> channels, inducing insulin secretion, mimicking the most common and severe monogenic form of congenital HI with K<sub>ATP</sub> channel inactivating mutations**

**Glucose sensing**
- ATP/ADP
- Glycolysis
- Amino acid metabolism

**Hypoglycemia**
- X

**Amino acid metabolism**
- Hypoglycemia

**K<sub>ATP</sub> channel**
- Depolarization
- Ca<sup>2+</sup> channel

**SST5 receptor**
- Inappropriate insulin secretion
CRN04777 Reversed SU-Induced Insulin Secretion in a Pharmacologic Model of Congenital HI

**Insulin Levels Following Sulfonylurea (SU) Challenge**

Data represent mean ± SEM; PBO: Placebo; QD: Once daily

* n=1 subject withdrew consent (not treatment related)
CRN04777 Reversed SU-Induced Hyperinsulinism in a Pharmacologic Model of Congenital HI

CRN04777 eliminated the need for IV glucose support by inhibiting excess insulin secretion.

**Glucose Infusion Rate (GIR) – Increases in Proportion to Insulin Secretion**

**Plasma Glucose (PG)**

Solid line in each figure represents the mean value; shaded area: SEM

* n=1 subject withdrew consent (not treatment related)
Dose-Dependent Reduction in IV Glucose Support Needed to Maintain Normal Blood Glucose Levels

CRN04777 inhibited SU-induced insulin secretion & eliminated the need for IV glucose support

Change in Insulin (AUC\(_{-55-120\text{min}}\))

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Insulin Reduction Compared to Baseline</th>
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<tbody>
<tr>
<td>Placebo (N=9)</td>
<td>31%</td>
</tr>
<tr>
<td>30 mg QD (N=6)</td>
<td>-40%</td>
</tr>
<tr>
<td>60 mg QD (N=6)</td>
<td>-74%</td>
</tr>
<tr>
<td>120 mg QD (N=5)*</td>
<td>-90%</td>
</tr>
</tbody>
</table>

Change in Glucose Infusion Rate (AUC\(_{0-10h}\))

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% GIR Reduction Compared to Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (N=9)</td>
<td>17%</td>
</tr>
<tr>
<td>30 mg QD (N=6)</td>
<td>-76%</td>
</tr>
<tr>
<td>60 mg QD (N=6)</td>
<td>-83%</td>
</tr>
<tr>
<td>120 mg QD (N=5)*</td>
<td>-97%</td>
</tr>
</tbody>
</table>

Data shown are mean ± SEM, reduction of each subject’s AUC on Day 10 vs. baseline (Day -2); SU: sulfonylurea; GIR: glucose infusion rate QD: once daily; AUC: area under the curve; * n=1 subject withdrew consent (not treatment related)
SU Challenge / Glucose Clamp Study Designed to Mirror the Congenital HI Patient Experience

Crinetics' goal is to obviate the need for IV dextrose and/or feeding tubes

**Mirroring Patient Experience**

- Sulfonylurea recapitulates the effects of the most common genetic mutations in congenital HI patients by stimulating excess insulin secretion.
- Without CRN04777, direct glucose support was needed to maintain glucose in the normal range, *modeling the experience of patients* who are dependent on glucose infusions (IV or enteral).

From Congenital Hyperinsulinism International's 2022 Feeding Tube Awareness Campaign
Conclusions from CRN04777 Phase 1 Program

Objectives:

• Evaluate Safety and tolerability
• Evaluate Drug-like pharmacokinetics
• Evaluate PK/PD for suppression of insulin secretion

CRN04777 was well tolerated in the Phase 1 program

Favorable pharmacokinetics results support once-daily dosing
• Rapidly absorbed after oral administration ($t_{\text{max}} \sim 1-3$ hrs.)
• Half-life of $\sim 40$ hours

Demonstrated pharmacologic proof-of-concept for SST5 agonism
• Dose dependent reduction in fasting insulin observed, which led to increases in fasting plasma glucose
• Dose-dependent reduction in glucose-induced insulin secretion achieved in an intravenous glucose tolerance test
• Dose-dependent reversal of sulfonylurea-induced insulin secretion achieved in a pharmacologic model of hyperinsulinism
Next Steps: Advancing Towards Program in Congenital HI Patients

1. Discuss program data package with global regulators

2. Initiate program in congenital HI patients (anticipated in 2H22)

3. Continued engagement with international congenital HI patient advocacy groups and Centers of Excellence
Pipeline Targets Multi-Billion $ Total Addressable Market with Internally Discovered Drug Candidates

NCE patent portfolio expected to provide protection into the 2040s

<table>
<thead>
<tr>
<th>PROGRAM</th>
<th>Development Stage (Potential Registrational Endpoints)</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td></td>
<td>Preclin</td>
<td>Phase 1</td>
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<td>----------------------------------</td>
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<tr>
<td>Paltusotine (SST2 agonist)</td>
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<tr>
<td>Acromegaly</td>
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<tr>
<td>Carcinoid Syndrome</td>
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<tr>
<td>Nonfunctional NETs</td>
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<tr>
<td>CRN04777 (SST5 agonist)</td>
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<tr>
<td>Congenital Hyperinsulinism</td>
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<tr>
<td>Syndromic Hyperinsulinism</td>
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<tr>
<td>CRN04894 (ACTH antagonist)</td>
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<tr>
<td>Congenital Adrenal Hyperplasia</td>
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<tr>
<td>Cushing’s Disease</td>
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<td>PTH antagonist</td>
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<tr>
<td>Hyperparathyroidism, HHM</td>
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**Spin-out company advancing nonpeptide precision radiotherapeutics targeting oncology indications.**

NETs: Neuroendocrine tumors; GIR: Glucose infusion rate; GC: Glucocorticoid; A4: Androstenedione; 17OHP: 17-hydroxyprogesterone; HHM: Humoral hypercalcemia of malignancy
## 2021 Accomplishments and Anticipated 2022 Milestones

<table>
<thead>
<tr>
<th>2021 Accomplishments</th>
<th>2022 Accomplishments &amp; Anticipated Milestones</th>
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<tbody>
<tr>
<td>✓ Initiated Ph 3 PATHFNDR program of paltusotide in acromegaly</td>
<td>✓ Strategic partnership for paltusotine in Japan</td>
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<tr>
<td>✓ Phase 1 POC data for CRN04894</td>
<td>✓ CRN04777 MAD data in 1Q22</td>
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<tr>
<td>✓ Phase 1 POC data for CRN04777</td>
<td>✓ CRN04894 MAD data in 2Q22</td>
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<td>✓ Launched Radionetics Oncology spinout</td>
<td>✓ CRN04777 patient study initiation in 2H22</td>
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<tr>
<td>✓ Strengthened balance sheet and extended cash runway into 2024</td>
<td>✓ CRN04894 patient study initiation in 2H22</td>
</tr>
<tr>
<td>✓ Identified potential development candidate PTHR1 antagonists for hyperparathyroidism and HHM</td>
<td>✓ Initiate IND enabling studies for PTHR1 antagonist</td>
</tr>
</tbody>
</table>

POC: Proof-of-concept; HHM: Humoral hypercalcemia of malignancy; MAD: Multiple-ascending dose