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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.
## Phase 1 Pharmacologic Proof-of-Concept for CRN04777 in Healthy Volunteers

<table>
<thead>
<tr>
<th>Safety Results</th>
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<tbody>
<tr>
<td>• Well-tolerated</td>
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<tr>
<td>• No Serious Adverse Events (SAEs)</td>
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<tr>
<td>• All Adverse Events (AEs) considered mild/moderate</td>
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<table>
<thead>
<tr>
<th>Pharmacokinetics Results</th>
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<tbody>
<tr>
<td>• Orally bioavailable with dose proportional pharmacokinetics</td>
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<table>
<thead>
<tr>
<th>Pharmacology Results</th>
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<tbody>
<tr>
<td>• Evidence of clinically meaningful suppression of insulin secretion</td>
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<tr>
<td>• Dose-dependent reduction in glucose-stimulated insulin secretion</td>
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<tr>
<td>• Dose-dependent reversal of sulfonylurea-induced insulin secretion (pharmacologic model of disease)</td>
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<th>Next Steps</th>
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<tr>
<td>• Progress to Multiple Ascending Dose cohorts</td>
</tr>
</tbody>
</table>
Crinetics’ Endocrine Development Strategy: Hormone Levels from Preclinical to Approval

**Preclinical POC**
Δ Glucose & Hormones, PK, Safety

**Phase 1 Healthy Volunteers**

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

**Phase 2/3 Trials (Patients)**

**Phase 1 Healthy Volunteer Safety, Pharmacologic POC**
Δ Glucose & Hormones, PK, Safety
Congenital Hyperinsulinism (HI) Results in Life Threatening Recurrent Hypoglycemia

Congenital HI patients secrete insulin even when blood sugar is low

Congenital HI is a devastating rare disease

- Untreated hypoglycemia can result in neurodevelopment disorders and death
- 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
CRN04777: First-in-class Oral SST5 Agonist with Potential to be Broadly Effective in HI

**Direct therapies**
- IV glucose
- Enteral dextrose (GT/NG)

**Liver Directed**
- IV glucagon, glucagon rescue pen
  - In development: Glucagon & Analogs (Subcutaneous)

**Pancreas Directed to suppress insulin secretion**
- Diazoxide
  - Ineffective in 50%; black box warning
  - Off label use of injectable SST2 agonists
  - Pancreatectomy (complete or partial)

**In development:**
- GLP-1 antagonist (IV)

**SST5 Receptor Agonist**
- CRN04777 in Phase 1
  - Designed to inhibit insulin secretion in all HI patients

**Target Tissue Directed to block Insulin Action**
- In development:
  - Insulin Receptor Antibody (IV)
Somatostatin Receptor SST5 Inhibits Insulin Secretion Downstream of all Known HI Causing Mutations

Syndromic hyperinsulinisms (e.g. those associated with Beckwith-Wiedemann syndrome, Sotos syndrome, Kabuki syndrome, and Turner syndrome) may also respond to SST5 agonism.
CRN04777 is the Only Oral SST5 Agonist in Clinical Development

CRN04777 is a potent (EC$_{50}$=0.4 nM) and selective SST5 agonist

CRN04777 suppressed sulfonylurea (SU)-induced insulin secretion and reversed hypoglycemia in rats
CRN04777 SAD Study Design to Evaluate Pharmacologic Proof-of-Concept

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

**Study Goals**
- Evaluate safety [0.5-120 mg]
- Evaluate pharmacokinetics: oral absorption, dose-proportional exposure, half-life [0.5-120 mg]
- Evaluate dose response and PK/PD on pre- and post-stimulated glucose and insulin in an IVGTT [0.5-120 mg]
- Evaluate dose response and PK/PD on reduction/reversal of sulfonylurea-induced insulin secretion (pharmacologic model of disease) [30-60 mg]

**Pharmacodynamic Assessments**
1. Intravenous Glucose Tolerance Test (IVGTT)
2. Sulfonylurea (SU) Challenge

**Proof-of-Concept**
- Dose dependent suppression of glucose-or sulfonylurea-induced insulin secretion with CRN04777
PK Results: CRN04777 Showed Oral Bioavailability with Dose-Proportional Exposure

Half-life ~40 hours and $t_{\text{max}}$ ~1-2 hours at efficacious doses

Data shown are mean±SEM; LLOQ = lower limit of quantitation
All doses n=6; except n=12 for 60 mg which was evaluated in both IVGTT and sulfonylurea challenge
*When 120 mg was administered within 30 minutes of a standard adult high fat breakfast, a significant reduction in exposure was observed. Evaluation of pediatric relevant meals pending.
CRN04777 SAD Study Designed to Evaluate Pharmacologic Proof-of-Concept

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

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**1. Intravenous Glucose Tolerance Test (IVGTT)**

Healthy volunteers received single oral dose of CRN04777 (n = 8, 6 active/2 placebo in each cohort)
CRN04777 Dose-Dependently Suppressed Glucose Stimulated Insulin Secretion

CRN04777 dose-dependently reduced insulin secretion stimulated by bolus IV glucose (IVGTT)...

...and reduced insulin secretion reduces glucose uptake by tissues resulting in prolonged elevation of plasma glucose

Data shown are mean±SEM
N=6 CRN04777 treated per dose; N=14 placebo
IVGTT=intravenous glucose tolerance test; PBO=placebo
CRN04777 SAD Study Designed to Evaluate Pharmacologic Proof-of-Concept

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

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**2. Sulfonylurea (SU) Challenge**

**Baseline (Day -2)**

- IV glucose
- “Glucose Clamp” with continuously adjusted glucose infusion rate (GIR)
- Multiple blood draws to measure glucose & insulin; Monitor GIR

**Treated (Day 1)**

- IV glucose
- “Glucose Clamp” with continuously adjusted glucose infusion rate (GIR)
- Multiple blood draws to measure glucose & insulin; Monitor GIR

Healthy volunteers received single oral dose of CRN04777 (n = 9, 6 active / 3 placebo in each cohort)
Sulfonylurea Challenge Provided Disease Relevant Proof-of-Concept

The administration of sulfonylurea is a pharmacologic model of congenital HI.

**Sulfonylurea Challenge**

- Sulfonylurea induces endogenous insulin secretion
- Automated delivery of supplemental IV glucose maintains blood glucose in the normal range (glucose clamp)
- Glucose infusion rate (GIR) increases in proportion to insulin secretion
CRN04777 reversed sulfonylurea-induced hyperinsulinism in a pharmacologic model of congenital HI

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

Glucose infusion rate (GIR) – increases in proportion to insulin secretion

More detailed data (insulin, C-peptide) to be presented at future medical conferences
Conclusions from CRN04777 SAD Results

Objectives

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

Safe and well tolerated at single doses from 0.5-120 mg

Achieved targeted pharmacokinetic profile
• Rapidly absorbed after oral administration ($t_{\text{max}} \sim 1-2$ hrs)
• Favorable half-life of $\sim 40$ hours observed
• Dose-proportional exposure from 0.5-120 mg

Demonstrated pharmacologic proof-of-concept for SST5 agonism
• 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
Pipeline With Three Candidates Beyond Pharmacologic Proof-of-Concept

<table>
<thead>
<tr>
<th>PROGRAM</th>
<th>Development Stage</th>
<th>Registralional Endpoint</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td></td>
<td>Preclin Phase 1</td>
<td>Phase 2 Phase 3</td>
<td>US Total</td>
</tr>
<tr>
<td>Paltusotine (SST2 agonist)</td>
<td>Pharmacologic POC</td>
<td>IGF-1 Levels</td>
<td>26K</td>
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<tr>
<td>Acromegaly</td>
<td></td>
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<tr>
<td>Carcinoid Syndrome</td>
<td></td>
<td>Diarrhea &amp; Flushing</td>
<td>33K</td>
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<tr>
<td>Nonfunctional NETs</td>
<td></td>
<td>Anti-tumor activity</td>
<td>138K</td>
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<tr>
<td>CRN04894 (ACTH antagonist)</td>
<td>Cortisol Levels</td>
<td></td>
<td>10K</td>
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<td>Cushing’s Disease</td>
<td></td>
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<tr>
<td>Congenital Adrenal Hyperplasia (CAH)</td>
<td>Adrenal Androgens/ Glucocorticoid use</td>
<td>27K</td>
<td>6.7 – 10.0</td>
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<tr>
<td>CRN04777 (SST5 agonist)</td>
<td>Glucose Levels/ Hypoglycemic Events</td>
<td>1.5-2K</td>
<td>0.64 – 1.3</td>
</tr>
<tr>
<td>Congenital Hyperinsulinism</td>
<td></td>
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<tr>
<td>Syndromic Hyperinsulinism</td>
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<td></td>
<td>2K</td>
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We continue to invest in ongoing discovery of new molecules targeting new indications with our in-house discovery team who are actively pursuing multiple programs in parallel. Indications include hyperparathyroidism, nonfunctional pituitary adenomas, polycystic kidney disease and more.
Achieved 2021 Goal of Three Programs with Clinical Proof-of-Concept

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<tr>
<th></th>
<th>1H21</th>
<th>2H21</th>
<th>1H22</th>
<th>2H22</th>
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<tbody>
<tr>
<td><strong>Paltusotine</strong></td>
<td>Initiate PATHFNDR-1</td>
<td>Initiate PATHFNDR-2</td>
<td>PATHFNDR-1 and PATHFNDR-2 Ongoing</td>
<td>Pathin PATHFNDR-1 and PATHFNDR-2 Ongoing</td>
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<tr>
<td>SST2 Agonist for Acromegaly &amp; NETs</td>
<td>POC Achieved</td>
<td>POC Achieved</td>
<td>POC Achieved</td>
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<tr>
<td>POC Achieved</td>
<td>Initiate P2 NETs Trial in Carcinoid Syndrome</td>
<td>Initiate P2 NETs Trial in Carcinoid Syndrome</td>
<td>Carcinoid Syndrome Phase 2 Ongoing</td>
<td>Carcinoid Syndrome Phase 2 Ongoing</td>
</tr>
<tr>
<td><strong>CRN04894</strong></td>
<td>Initiate Phase 1</td>
<td>Phase 1 POC SAD Data</td>
<td>Phase 1 MAD Data(Q1)</td>
<td>Initiate Phase 2 in Patients</td>
</tr>
<tr>
<td>ACTH Antagonist for Cushing’s Disease &amp; CAH</td>
<td>POC Achieved</td>
<td>POC Achieved</td>
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<tr>
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<td>Initiate Phase 1</td>
<td>Phase 1 POC SAD Data</td>
<td>Phase 1 MAD Data(Q1)</td>
<td>Initiate Phase 2 in Congenital HI Patients</td>
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<tr>
<td>SST5 Agonist for Congenital HI</td>
<td>POC Achieved</td>
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Executed development strategy with three NCEs: paltusotine, ‘4894, and ‘4777