CSI Glucagon™ for Treatment of Severe, Persistent Hypoglycemia

CHI Annual Conference
Galloway, NJ
August 16-17, 2014
HYPOGLYCEMIA AND GLUCAGON

» Hypoglycemia – the unmet need
» Glucagon’s role in treatment of hypoglycemia...historically limited....why?
» How room temperature stable glucagon is meeting the need
» Xeris’ CSI (Continuous Subcutaneous Infusion) Glucagon™ development program for HI
OUR COMPANY

• Located in Austin Texas
• Office & laboratory facilities on north side of University of Texas campus
• Currently 15 employees and contractors
• CMC, toxicology, regulatory & drug development experience
• Our r&D efforts are focused on formulation discovery and screening in house – e.g. room temperature stable monomeric insulin
• Raising $5M to fund development programs

3208 Red River Street, 3rd Floor
Austin, Texas
Glucagon - the counter-regulatory hormone to insulin

- Natural hormone responsible for raising blood sugar
- Works in tandem with insulin to regulate blood sugar
- Only outpatient treatment for severe hypo (emergency rescue)
UNMET NEED: HYPOGLYCEMIA

XeriSol Glucagon (5 mg/ml)

G-Pen™ Severe Hypo

G-Pen Mini™ Moderate hypo

G-Pump–AP™ Bionic Pancreas

G-Pump–HRH™ High-Risk Hypo

CSI Glucagon™ Congenital Hyperinsulinism

Xeris Pharmaceuticals, Inc.
Severe Physical & Emotional Burden

- Diabetics live with the fear of hypoglycemia on a daily basis
- Parents worried about their kids at night when risk of hypoglycemia is greatest
- Lack of easy treatments for severe/moderate hypoglycemia makes social interaction (sleepovers, camping trips, etc.) difficult for kids, leading to isolation and stigma
- Latest report from ADA Working Group on Hypoglycemia demonstrates significant morbidities and mortality associated with hypoglycemia

Piper has Type 1 diabetes.*

One in twenty people like Piper will die from low blood sugar.*

* From NY Times ad placed by the JDRF

21M diagnosed diabetics
8.1 undiagnosed
(CDC 2014)

6M insulin dependent

300M hypo events/yr

3.3M severe events/yr
Severe Physical, Emotional Burden

- **Parents worry about their kids 24/7** - risk of hypoglycemia is constant
- **Kids live with the fear of hypoglycemia on a daily basis**
- **Lack of care-giver and patient-friendly treatments for HI makes social interaction (sleepovers, camping trips, etc.) difficult for kids, leading to isolation and stigma**
- **Staggering financial impact on families**

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*Piper has Congenital Hyperinsulinism.....*

Approximately 30% of HI kids will suffer some neurological dysfunction from their severe, persistent hypoglycemia

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Est. 170 diagnosed annually in US

- **50% Focal**
  - 95% surgical cure

- **50% Diffuse**
  - 50% Diazoxide Rx
  - 50% Surgical Rx or Medical Mgt.

90% of pancreatectomies lead to insulin dependence by age 14

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The FDA can help treat and cure those with HI
GLUCAGON’S HISTORICALLY LIMITED ROLE IN TREATING HYPOS – ITS INSTABILITY WATER!

- Poor stability
- Poor solubility
- Complicated formulations
  - Reconstitution/Refrigeration
  - Large volumes, painful
- Poor products
- Poor access
- Poor compliance
Simplifying the formulation
Can eliminate many ingredients often required in water-based formulations

Co-formulation
Process allows two drugs to be combined in the same formulation in a way not before possible

Intellectual Property
Xeris has intellectual property at each step of formulation

Xeris Pharmaceuticals, Inc.
Previous Use of Glucagon in treating severe, persistent hypoglycemia with HI

» Mohnike et al. 2008 reported a retrospective review of 9 HI patient cases where continuous subcutaneous (SC) glucagon was used as a treatment option (1 – 3 mg/day), with or without concomitant octreotide and IV glucose.

The objectives of using continuous SC glucagon were to:

» Stabilize blood glucose levels for several weeks without the use of high-volume dextrose infusions administered via a central catheter, which often causes bloating, and

» Avoid pancreatectomy or resurgeries (further reduction of pancreatic tissue) in patients with diffuse HI.
OUTCOMES WITH SC GLUCAGON

» Central glucose infusions significantly reduced or eliminated in all 9 children

» SC glucagon continued in 3 of 6 children for 1-4 years without further symptomatic hypoglycemia, convulsions or unconsciousness

» Glucagon treatment was initiated to manage recurrent hypoglycemia after subtotal pancreatectomy in 2 of 9 children

» Pancreatectomy or resurgeries were avoided in 5 of 9 children

» Octreotide was reduced to 8-15 μg/kg/day – considerably lower than if given alone, without glucagon (15-60 μg/kg/day)

» An experimental, stabilized glucagon (glucagon Technosphere™ suspension) was IRB approved and used successfully in 3 children – a peek at the future
G-PEN™ STABILITY @ ROOM TEMPERATURE

Glucagon Assay (RP-HPLC)
FFM-12-019 (Engineering Batch)
20-25°C Storage

y = -0.5739x + 98.987
R² = 0.9696

Upper Confidence Interval (95%)
Nominal Specification (80%)
Lower Confidence Interval (95%)
USP Specification (65%)

Glucagon Content (%)

Time (months)
CSI GLUCAGON™ STABILITY IN OMNIPOD® PATCH-PUMP

Study Highlights

• Testing with both RP-HPLC and SE-HPLC showed high glucagon purity maintained over 6-days inside the OmniPod® stored at 37C

• G-Pump™ Glucagon remained clear and free of particulates over 6 days inside the OmniPod® stored at 37C

• No significant findings observed in UV spectrum from 350 – 650 nm
» No Statistically Significant Differences in AUC, $T_{\text{MAX}}$, and $C_{\text{MAX}}$ (full dose)
CSI GLUCAGON™ + OMNIPOD™ PATCH PUMP FOR HI

CSI Glucagon™

Xeris Pharmaceuticals, Inc.
PIG PK/GLUCODYNAMICS STUDY DESIGN

» Conducted at OHSU Legacy Research Institute
» Flurane anesthetized female Yorkshire Pigs (35-50 kg)
» Insulet OmniPod® inserted on abdominal skin
» 2 µg/kg of:
  ➢ Xeris fresh Glucagon (N=8)
  ➢ Xeris 7-day aged Glucagon (N=8)
  ➢ Novo GlucaGen® (N=8)
» Blood obtained at baseline and 10 points over 2 hours
» Serum collected for glucose and glucagon analysis
CSI GLUCAGON™ PIG STUDY

Pharmacodynamics of glucagon preparations:
Xeris fresh, Xeris aged, Novo Glucagen
mean ± SEM (n = 8)

Xeris, fresh
Xeris, aged
Novo

blood glucose
(rise above baseline, mg/dl)

0 50 100 150 200 250

0 20 40 60 80 100

0 20 40 60 80 100

X Aged
X fresh
NOVO

Xeris Pharmaceuticals, Inc.
G-PUMP™ GLUCAGON CLINICAL PLAN

Phase 2a Inpatient Dose-Ranging Study

- 18 diabetic patients on insulin clamp
- Three randomized micro-doses of G-Pump™ Glucagon from OmniPod® pump on same day
  - Ward et al glycogen depletion study
- Same doses with Novo GlucaGen® comparator on Day 2
- Enrollment completed!

Phase 2b Outpatient Closed-Loop (Hotel Study)

- 30-hour closed-loop study with CGM, insulin pump, glucagon pump, OHSU adaptive control algorithm
- Hotel near OHSU campus with nurse nearby
- Amendment to Castle/Ward open IDE
Study Highlights

- Study conducted in diabetic pigs by Dr. Edward Damiano at Boston University
- Xeris glucagon administered via pump strapped to pig
- Glucagon subjected to higher temp and agitation for 7 days
- Basal insulin + bolus at T = 0 starts to bring glucose down
- Demonstrated glucose boosting effect at 7 days not possible with Lilly glucagon
The study contemplates an approximately 3-4-day in-patient phase in which CSI Glucagon™ is integrated into a medical management program with IV glucose and/or somatostatin to stabilize a patient’s blood glucose levels.

Medical management goals are:

- To decrease IV glucose feeds and/or somatostatin utilization (both of which have their own adverse effects),
- To increase fasting intervals.

Out-patient Phase

Patient will be discharged to an out-patient setting – once goals are met for the remainder of the 180-day period.

Patient will continue on CSI Glucagon™ indefinitely after 180 days, if clinical goals continued to be met until sufficient complex carbohydrates can be integrated into their diet, whereupon glucagon treatment can be tapered and eventually discontinued.
CLINICAL SITES FOR EARLY 2015 HI TRIAL

Great Ormond Hospital (London)
Royal Manchester Children’s Hospital
Children’s Hospital of Philadelphia
(Magdeburg, Germany)
Cook Children’s Hospital
(Fort Worth, TX)
Texas Children’s Hospital
(Houston, TX)
Hadassah Medical Center
(Jerusalem, Israel)
# THE POTENTIAL FOR CSI GLUCAGON™ IN TREATING HI

<table>
<thead>
<tr>
<th></th>
<th>Current Std. of Care</th>
<th>Potential with Pump-G</th>
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<tbody>
<tr>
<td><strong>In Patient</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical Mgt. of Blood Glucose</td>
<td>Octreotide and dextrose feed</td>
<td>↓↓ or discontinued</td>
</tr>
<tr>
<td>Surgery</td>
<td>Unchanged</td>
<td>↓ - more parents may elect for medical management not surgery</td>
</tr>
<tr>
<td>Time in hospital</td>
<td>Unchanged</td>
<td>↓ - faster to stable glucose levels and discharge to out-patient care</td>
</tr>
<tr>
<td>Costs</td>
<td>Unchanged</td>
<td>↓ - faster to medical management and discharge</td>
</tr>
<tr>
<td><strong>Out Patient</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical Mgt</td>
<td>Octreotide and Dextrose Feed</td>
<td>Reduced or never started</td>
</tr>
<tr>
<td>Risk of severe hypos</td>
<td>Unchanged</td>
<td>↓↓</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Unchanged</td>
<td>↑↑</td>
</tr>
<tr>
<td>Costs</td>
<td>Unchanged</td>
<td>↓↓</td>
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**GLUCAGON DEVELOPMENT STATUS**

- **G-Pen™**
  - Phase 2 completed – FDA EOP2 meet JUL14

- **G-Pen Mini™**
  - IND cleared 12/13; Phase 2 start in April

- **G-Pump AP™**
  - IND cleared 01/14; Phase 2 start in April

- **G-Pump HRH™**
  - IND cleared 01/14

- **CSI Glucagon™**
  - FDA Pre-IND Meeting 3Q14*

*Complete*  |  *In-Process*

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*Orphan Drug designation application submitted to FDA June 2014; European Medicines Agency July 2014*
$5.7M received in non-dilutive research and development grants

Xeris Pharmaceuticals, Inc.
A PARENT & PATIENT-FRIENDLY SOLUTION FOR THE HI COMMUNITY