A novel glucagon/GLP-1 dual agonist partnered with Boehringer Ingelheim in T2D/obesity

By Christian Grøndahl, EVP and Chief Scientific Officer

Capital Markets Day, NYC — 29 November 2012
TYPE-2 DIABETES AND OBESITY GO HAND IN HAND

THE GLOBAL HEALTH CHALLENGE: DIABETES AND OBESITY EPIDEMIC

• Worldwide, 1 billion people are overweight, and of these 300 million are obese
  – Rates are increasing, in particular in South America, India, the Middle-East and China

• Obesity plays a significant role in the pathogenesis of Type 2 diabetes (T2D)
  – Approx. 90% of people with T2D are overweight/obese
  – Excess fat tissue increases insulin resistance and complicates the treatment of T2D

• Weight loss can reverse T2D
  – An 11% reduction in body weight is associated with a 25% reduction in cardiovascular disease and diabetes mortality
Associated Complications of Diabetes
- Diabetic retinopathy
- PAD (Peripheral Artery Disease)
- Diabetic neuropathy
- Gut inflammation and malabsorption
- Alzheimers Disease

Beta-cell function and regeneration
- More effective glucose handling
- Formation of new islets

Gastric sensing
- GI-tract nutrient sensors controlling the release of gut hormones
- Gastric emptying
- Appetite control
- Mimicking the effects of gastric bypass

Weight management
- Increase in energy expenditure
- Increase in fat metabolism
- Therapies for maintaining a healthy BMI
OXYNTOMODULIN, GLP-1 AND GLUCAGON ARE ALL PRODUCTS OF PROGLUCAGON - AND ALL PLAY A ROLE IN METABOLISM

Major, characterised patterns of proglucagon activity:

Regardless of activity, each of these peptides is secreted into blood after ingestion of a meal containing carbohydrates or lipids.
Oxyntomodulin

- Is secreted from L cells in the small intestine in response to meal ingestion
- Identical to glucagon but with an 8-amino acid extension
- Binds the glucagon receptor with low affinity relative to glucagon
- Short in vivo half-life
- Has been demonstrated to induce significant body weight loss in human obese subjects
- Believed to induce weight loss through activating both the GLP-1 and the glucagon receptor (i.e. by dual glucagon-GLP-1 agonism)

OXYNTOMODULIN HAS SHOWN BENEFICIAL EFFECTS

Decrease food intake

Increase energy expenditure

Wynne et al. (2005) Diabetes; 54:2390–2395

OXYNTOMODULIN, GLP-1 AND GLUCAGON ARE ALL PRODUCTS OF PROGLUCAGON - AND ALL PLAY A ROLE IN DIABETES

<table>
<thead>
<tr>
<th>Proglucagon</th>
<th>Gut</th>
<th>Pancreas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-Translational Splicing</td>
<td>Oxyntomodulin</td>
<td>GLP-1</td>
</tr>
<tr>
<td></td>
<td>Glucagon</td>
<td>GLP-1 + Glucagon</td>
</tr>
</tbody>
</table>

- Zealand Pharma has used glucagon as the basis for transforming a sequence of 1-29 into a dual GLP-1-glucagon agonist with the characteristics of oxyntomodulin.
- This approach has yielded ZP2929, a more potent peptide than Oxyntomodulin.
- ZP2929 is cost effective to produce.
GLP-1 is potent ONLY on the GLP-1 receptor – no potency on the glucagon receptor

Oxyntomodulin is potent mainly on the glucagon receptor and less on the GLP-1 receptors

ZP2929 is highly potent on BOTH the glucagon receptor AND the GLP-1 receptor
ZP2929: PRE-CLINICAL PROOF-OF-CONCEPT ESTABLISHED

**Significant Improvement of Glucose Control**

Diabetes model (db/db mice)

- HbA1c (% relative to day 0)
- Days of Treatment: 7, 14, 21, 28, 35, 42
- ZP2929 (△)
- Marketed GLP-1 agonist (●)
- Placebo (○)
- *p<0.05

**Significant and Sustained Weight Loss**

Obesity model (Diet Induced Obese (DIO) mice)

- Body Weight Gain (g)
- Days of Treatment: 0, 7, 14, 21, 28, 35, 42
- n = 9-10
- ***p<0.001

Diabetes model (db/db mice) and Obesity model (DIO mice) demonstrate significant and sustained improvements in glucose control and weight loss, respectively. ZP2929 shows promise as a potential therapeutic agent in these models.
THE FIRST PHASE I STUDY

A randomized, double-blind, first in human study to evaluate the safety and tolerability of ZP2929 in healthy volunteers

Conducted by Zealand Pharma in the US under an IND with the FDA

STUDY DESIGN

• Primary endpoints
  Safety and tolerability measures

• Secondary endpoints
  Pharmacokinetics and immunogenicity

• Dosing regimens
  Single ascending daily sub-cutaneous dosing (SAD)

• Enrollment
  Healthy volunteers
Leveraging Zealand’s peptide competences into expansion of the metabolic pipeline
By/ Christian Grøndahl, EVP and Chief Scientific Officer

Capital Markets Day, NYC - 29 November 2012
ZEALAND’S FIRST DUAL AGONISTS IN DIABETES/OBESITY

ZP2929

Glucagon + GLP-1

Glucose control (equivalent to a GLP-1 agonist)

Superior and sustained weight loss (compared to treatment with GLP-1 agonist alone)

ZP3022

GLP-1 + GASTRIN

Superior and Sustained effect of GLP-1-gastrin on β-cell mass compared to marketed GLP-1s

Superior and sustained effect on glycemic control compared to GLP-1 analogues

Translation into Human medicine is the next step
GLP-1-GASTRIN DUAL ACTING PEPTIDES

EFFECTS ON PANCREATIC β- CELLS

Pancreas

Endocrine part
Islets of Langerhans

β-cell preservation and regeneration

Insulin producing β-cells

Glucagon producing α-cells

GLP-1/Gastrin peptides

WHAT DO WE KNOW FROM THE LITERATURE?

On GLP-1
- Increased glycemic control in T1DM and T2DM Varanasi 2011

On GASTRIN
- Improved glycemic control 6 month post treatment in T2DM Transition Therapeutics

On GLP-1 + GASTRIN
- Marked preservation of β-cell mass in db/db mice Tamaki et al., 2010
- Increase in β-cell mass and improved glycemic control in NOD mice Pinzon et al 2008, WO2007095737
- A loose combination of the compounds induces beta cell neogenesis in human islets transplanted in NOD SCID mice Pinzon et al 2008
GLP-1-GASTRIN DUAL AGONISTS – EFFECT ON BLOOD GLUCOSE

Effects of GLP1-Gastrin dual agonist, ZP3022 vs. liraglutide on blood glucose following different treatment paradigms (db/db mice):

CONTINUOUS TREATMENT

LATE TREATMENT

EARLY TREATMENT, DRUG HOLIDAY

Results for ZP3022 in a drug holiday setting indicates that the effect on blood glucose of GLP-1/gastrin dual agonists is durable and different from pure GLP-1 agonists

Fosgerau et al., DOM 2012 (in review)
The effect of GLP1-Gastrin dual agonist ZP3022 vs. liraglutide following different treatment paradigms (Oral Glucose Tolerance Test, db/db mice):

**CONTINUOUS TREATMENT**

**LATE TREATMENT**

**EARLY TREATMENT, DRUG HOLIDAY**

Results for ZP3022 in a drug holiday setting indicates that the effect on blood glucose of GLP-1/gastrin dual agonists is durable and different from pure GLP-1 agonists.

Fosgerau et al., DOM 2012 (in review)
The effects of GLP-1-Gastrin dual agonist ZP3022 vs. liraglutide on HbA1c and Islet/β-cell mass in db/db mice following 3 weeks treatment

Fosgerau et al., DOM 2012 (in review)
TRIPLES
- The potential next step in diabetes/obesity management

Glucagon
(Body Weight, Energy Expenditure)
GLP-1
(HbA1c lowering)

GIP
(HbA1c, Body Weight)
Gastrin
(Beta-cell mass)
CCK
(Ob/ Food intake)
PYY
(Body Weight)
GLP-2
Inflammation NAFLD Endotoximia
Amylin
(Diabetes)
BUILDING ZEALAND PHARMA’S METABOLIC PIPELINE

Lixisenatide (Lyxumia®) - Once-daily GLP-1
- 16 Nov’12; Positive CHMP recommendation for approval in EU
- 12 regulatory filings, incl Japan in 2012, US filing planned for Dec’12

Glycemic Control

Glycemic Control (Oral administration)

ZP2929 (Glucagon/GLP-1 dual agonist)
- Phase I study started in Sept’12

GLP-1 Gastrin dual agonist

Glycemic Control + CVD/LIPID

Novel dual/triple acting peptide drugs

Glycemic Control + Beta-cell mass

Orally acting peptide drugs

Glycemic control + loss of body weight

POTENTIAL CLINICAL ATTRIBUTES

Lixisenatide + Lantus® fix/flex combination
- Phase III start expected mid-2013

Glycemic Control

TIME

PRODUCTS

VALUE