Type them into questions box!

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23/10/2019
7
THIS ACS WEBINAR WILL BEGIN SHORTLY...

Treating Diabetes: Designing the Once-Weekly and Oral GLP-1 Semaglutide

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This ACS Webinar is co-produced with the ACS Division of Medicinal Chemistry, American Association of Pharmaceutical Scientists, and ACS Publications
Designing the Once-Weekly and Oral GLP-1 Semaglutide

Jesper Lau
Vice President
Novo Nordisk

Audience Survey Question
ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

What is Glucagon-like-peptide-1?

• A long acting artificial synthetic peptide
• A 32 amino acid natural peptide hormone
• A peptide released from the L-cells
• A peptide that increases appetite

* If your answer differs greatly from the choices above tell us in the chat!
Native GLP-1 has limited clinical value because of its short half-life

PK data adapted from Vilsbøll et al. J Clin Endocrinol Metab 2003;88:220–224

Native GLP-1 must be administered continuously to realise full therapeutic potential

Blood glucose profiles:  
- Intermittent (16 h/day) GLP-1 i.v. infusion (8 ng/kg/min)  
  (n=8)  
- Continuous (24 h/day) GLP-1 i.v. infusion (8 ng/kg/min)  
  (n=8)  

Adapted from Larsen et al, Diabetes Care 2001;24:1416–1421.

PBS, phosphate-buffered saline.
Bayliss and Starling proposed that intestinal mucosa contained a hormone which stimulated the exocrine secretion of the pancreas.

**Discovery of the Insulinotropic Effect of GLP-1**

Bayliss and Starling proposed that intestinal mucosa contained a hormone which stimulated the exocrine secretion of the pancreas.

**Early clinical potential**

<table>
<thead>
<tr>
<th>Year</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1902</td>
<td>Keymann, Williams, Ghatai and Bloom, Lancet 1987;1300-1303</td>
</tr>
<tr>
<td>1989</td>
<td>Nauck, Kleine, Ørskov, Holst, Wills and Creutzfeldt, Diabetologia 1993;36:741-744</td>
</tr>
</tbody>
</table>

**First two GLP-1 RA approvals**

2005 and 2009

**Human proglucagon gene was cloned**

Bell, Nature 1983;302:716-718

**GLP-1 receptor cloned**

Thorens, PNAS 992;89:8641-45

**First two GLP-1 RA approvals**

2005 and 2009

**GPCR class B structures**

1989

1997

2005

2017

**Key puzzle for successful GLP-1 engineering**

Convenience

Easy to use
Once weekly GLP-1: Parallel explorations of protraction enablers

Several strategies have been explored by industry:

- **Sustained release:**
  - Bydureon (BMS/AstraZeneca), Taspoglutide (Roche/Ipsen)

- **Fusion proteins:**
  - Albiglutide (GSK)
  - Dulaglutide (GLP-1 Fc, LY2189265, Lilly)
  - GLP-1 transferrin (PF-4856883, Pfizer)

- **Pegylation:**
  - GLP-1 PEG (Lilly)

- **Reversible albumin binding**
  - Semaglutide (Novo Nordisk)

Human serum albumin

- Is a large (>60kDa) natural human protein
- Circulates in the blood in high concentrations (~40mg/ml)
- Has a long plasma T½ (3 weeks)
- Binds fatty acids reversibly (transport and solubility)
Liraglutide obtains a once-daily profile by reversible binding to albumin

PK parameters
- $T_{\text{max}}$: 9–12 h
- $T_{1/2}$: 11–15 h
- Bioavailability: 55%

Adapted from Elbrønd et al. Diabetes Care 2002;25:1398–1404. $n=72$ ($n=8$ for each dose)

Four key hurdles to engineering a superior once-weekly GLP-1

1. Albumin binding (limiting renal elimination)
2. Access to the right target tissues
3. DPP-IV stability
4. Maintain high receptor affinity

Linker exploration of GLP-1

Prolonging the half-life from once-daily to once-weekly by fatty acid exploration

Fatty acid

GLP-1R potency (EC50 pM)

Systemic half-life increases - with increasing length of di-acid

7 Days duration of action of semaglutide
- in mini pigs, hyperglycaemic clamp

Efficacy and duration of action of semaglutide
- in LYD pigs

- **Effect on appetite in LYD pigs:**
  - Dose dependent effect on appetite
  - 7 days duration of action

unpublished
GLP-1 Once-daily vs Once-Weekly
- Minor Structural differences

Liraglutide

H₂N-HAEGTFTSDVSSYLEGQAAKEFIAWSLVGRG-COOH

Semaglutide

H₂N-HXEGTFTSDVSSYLEGQAAKEFIAWSLVGRG-COOH

Semaglutide was selected as once weekly lead
- based on animal data

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide</th>
<th>Semaglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini pig s.c. availability</td>
<td>66%</td>
<td>94%</td>
</tr>
<tr>
<td>MRT minipig (s.c. dosing)</td>
<td>23hrs</td>
<td>64hrs</td>
</tr>
<tr>
<td>In vivo potency (db/db mice)</td>
<td>6.9 nmol/kg</td>
<td>0.3 nmol/kg</td>
</tr>
<tr>
<td>T½ humans (s.c. dosing)</td>
<td>13hrs</td>
<td>?</td>
</tr>
<tr>
<td>Expected Human dose</td>
<td>&lt;2mg/day</td>
<td>&lt;2mg/week</td>
</tr>
</tbody>
</table>
Semaglutide has an optimal pharmacokinetic profile for once weekly dosing...

Simulation of pharmacokinetic profile

Semaglutide is the result of a few smart modifications to the human GLP-1 molecule

Fatty acid optimisation for strong albumin binding, NN protein chemical engineering

OEG linker for peptide flexibility and optimised binding to receptor

H₂N−HXEGTFTSDVSSYLEGQAAKEFIAWLVRGRG−COOH

Aib is an unnatural amino acid for preventing peptidase degradation

Peptide chain based on liraglutide discovery (human GLP-1):
NN protein chemical engineering and alanine scan
Once-weekly semaglutide provides unprecedented glucose regulation...

... and unprecedented weight loss
...and a highly selective binding to the human GLP-1 receptor

Binding site defined primarily by ECD, ECL1, TM1, TM2 and TM7

GLP-1 almost entirely α-helical in the receptor-bound state

Why is semaglutide different?
Continuous plasma exposure with little fluctuation and higher concentration in specific area of the appetite centre

Simulated pharmacokinetic profiles

Normalized plasma concentration (%)

Time at steady state (days)

semaglutide once weekly
liraglutide once daily
lixisenatide once daily

Chronic administration

PK modelling
Semaglutide - a convenient once-weekly GLP-1 with superior blood glucose regulation

Semaglutide
- is an analogue of human GLP-1
- has a once weekly profile through binding to albumin
- has a high potency and long duration of action in animals which translate to an excellent profile in humans
- holds great opportunity for oral administration

At a new cross road:
Oral peptide and protein delivery
Which statement is wrong? **Oral GLP-1 peptide delivery is a challenge due to:**

- Enzymatic degradation in the intestinal tract
- The intestinal uptake due to the size of the peptide
- The clinical trials are very difficult
- An absorption enhancer may be required

*If your answer differs greatly from the choices above tell us in the chat!*

There are many barriers to oral protein delivery

**Avoiding degradation**

The gastro-intestinal tract is designed to degrade proteins by enzymes and low pH

**Reaching epithelial cells**

Proteins are lipophobic: no passive transport through the intestinal wall

**Absorption to blood**
Oral delivery platforms

Eligen®

SNAC

GIPET®

SNAC is an enhancer that facilitates absorption. The available data for semaglutide co-formulated with SNAC support that absorption takes place in the stomach in a localised buffered environment. The effect is strictly time- and size-dependent and occurs primarily via trans-cellular route.
Stomach is the predominant site of absorption
Highest concentration of semaglutide observed in vena linealis in dogs

**Plasma concentration of semaglutide after 10 mg oral dose in dogs**

Semaglutide levels were higher in the splenic vein over the first 30 min after dosing (AUC$_{0-30\text{min}}$ splenic/portal: 1.9)

Complete tablet erosion of oral semaglutide occurs in the stomach
Scintigraphic imaging of an indium-111 labelled tablet

- Mean time to complete tablet erosion was 85 minutes (95% CI: [62;118])
SNAC carrier facilitates semaglutide absorption

SEMGLUTIDE

SNAC: Sodium N-[2-(2-hydroxybenzoyl) Amino] Caprylate

Oral semaglutide dose dependently reduced HbA$_{1c}$ and body weight in phase 2 trial

HbA$_{1c}$ reduction from a mean baseline of 7.9%

- Placebo
- sema 2.5 mg
- sema 5 mg
- sema 10 mg
- sema 20 mg
- sema 40 mg
- sema 1 mg SC

Weight loss from a mean base line of 92 kg

Data on graph are estimated mean +/- standard error of the mean
SC: subcutaneous; Sema: semaglutide
Main inclusion criteria: Type 2 diabetes; 7.0% ≤ HbA$_{1c}$ ≤ 9.5%; Treatment with diet and exercise
+/- metformin
Source: Trial NN9924-3790
Conclusion

Semaglutide:

- Is a once weekly GLP-1 analog that binds to albumin
- Is an analog of human GLP-1
- Was selected as once weekly candidate based on long duration of action in pigs
- Once weekly profile was confirmed in humans
- Has now shown great opportunity for both once weekly dosing and oral treatment

Thanks to the Semaglutide Team

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