STRATEGIES FOR INCREASING PEPTIDE PLASMA EXPOSURE TIME AS SEEN THROUGH THE LENS OF THE GLP-1 CLASS

GSK-CRS LONG ACTING INJECTABLES MEETING
18 APRIL 2017

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PRESIDENT AND CEO
PRESENTATION OUTLINE

• Delivery Technologies for Sustained Exposure of Peptides
• Target Product Profile and Decision-Making on Technology
• GLP-1 Class As an Example of Broad Technology Utility
• Exenatide and Its Life Cycle
**Market Preference for Injection Frequency**

**Decreasing Injection Frequency**

- Multiple Daily Inj
- Daily Injection
- Weekly Injection
- Monthly Injection
- Quarterly Injection
- 6 to 12 Month Inj

**Patient Self-Injection Common:**
Product Profile More Critical

**Product Profile Parameters**
- Complexity of product handling
- Ready-to-use product
- Needle size for injection (viscosity)
- Injection force (viscosity)
- Pain on injection (volume)
- Duration of injection (volume)
- In-Use stability constraints

**Potential for Office Administered Product:**
Good Product Profile
Not Critical
Peptide Sustained Release Formulation Strategy

Molecule
- Efficacy / side effects
- Continuous or pulsatile
- Cost per gram
- Physicochemical properties

Formulation
- Process complexity / scale-up
- Bioavailability / efficiency
- Cost for process / fill / finish
- Compatibility with molecule

Device
- Device complexity
- Ease of use / acceptance
- Cost per unit
- Formulation compatibility

Biology & Chemistry
PK & Formulation
Device & Handling

Area of Emphasis and R&D Work
Molecular Engineering Strategy for Peptides

Covalent Analogue
- Efficacy and half-life
- Complexity of process
- Cost per gram
- PK Profile

Formulation
- Formulation concentration
- Viscosity of solution
- Cost for process / fill / finish
- Compatibility with molecule

Device
- Device complexity
- Ease of use / acceptance
- Cost per unit
- Formulation compatibility

PK PD Confirmation

Device & Handling

Area of Emphasis and R&D Work
Decision is often based on the status of the program and the focus of the company running the program, along with technical factors.

- **Molecular Engineering:** SAR program requiring chemistry, biology, PKPD
- **Sustained Release Formulation:** Formulation program requiring PK work and PD confirmation

Typically new analogues in well established Pharmacology (e.g. GLP-1 class)

Typically development molecules or commercialized products
<table>
<thead>
<tr>
<th>TECHNICAL FACTORS FOR DELIVERY STRATEGY CHOICE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daily injection dose may drive decision</strong></td>
</tr>
<tr>
<td>- 0.01 to 1 mg/day = multiple strategies feasible</td>
</tr>
<tr>
<td>- 10 mg/day = covalent strategy more likely</td>
</tr>
<tr>
<td>- Bulking up of mass can be a problem, PEG &lt; 10 mg</td>
</tr>
<tr>
<td><strong>Molecular engineering often preferred where recombinant manufacturing would be advantage</strong></td>
</tr>
<tr>
<td>- Ex. xten, elpylation, Fc, albumin, ABD conjugates</td>
</tr>
<tr>
<td><strong>Half-life requirement for formulation strategy</strong></td>
</tr>
<tr>
<td>- &gt; 30 minutes half-life in human = formulation strategy</td>
</tr>
<tr>
<td>- &lt; 30 min half-life = covalent half-life extension strategy</td>
</tr>
</tbody>
</table>
SUSTAINED RELEASE FORMULATION TECHNOLOGY

In Situ Gel-Forming System

Weekly Injection

Daily Injection

Increasing Drug Potency

Suspension

Liposome

Microsphere

Non-Aqueous Solution/Suspension

Implant

Atrigel

SUSTAINED RELEASE FORMULATION TECHNOLOGY

Daily Injection

Weekly Injection

Monthly Injection

Quarterly Injection

Suspension

Liposome

In Situ Gel-Forming System

Microsphere

Non-Aqueous Solution/Suspension

Implant

Atrigel
COVALENT HALF-LIFE EXTENSION TECHNOLOGY

Increasing Drug Potency

Daily Injection
- Acylation (albumin binder)

Weekly Injection
- Carbohydrate analogues
- XTEN, ELP, PASylation
- PEGylation

Monthly Injection
- HESylation, Glycosylation
- Various including Reversible PEG
- Albumin or Fc Fusion (FcRn recycling)

Different injection frequencies:
- Daily Injection
- Weekly Injection
- Monthly Injection

Increasing Drug Potency
EXENATIDE DISCOVERED BY JOHN ENG AS AMIDATED PEPTIDE
LICENSED TO AMYLIN 1996 AFTER PUBLISHING GLUCOSE REDN
Launched by Amylin and Eli Lilly Partnership (now owned by Astra Zeneca)

Exenatide
Drug substance
39 amino acid peptide

Exenatide Injection
1.2 & 2.4 mL cartridge for injection
0.25mg/mL strength

Exenatide Disposable Pen-injector
5 mcg or 10 mcg per injection
2 year shelf-life
30 day in-use period at RT

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GLP-1s Move to Maximize Continuous Exposure

Exenatide (Byetta)
Half-life 1-2 hrs

Liraglutide (Victoza)
Half-life 13 hrs

-0.9%

HbA1C Reduction

-1.2%

-1.5%


US 2005
EU 2006

EU 2009
US 2010

EU 2011
US 2012


Exenatide MS (Bydureon)

Adapted from Elbrand et al. Diabetes Care 2002;25:1398-1404. (n=5 for each dose)

Kim D et al. Dia Care 2007;30:1487-1493
GLP-1 AGONIST MOLECULAR ENGINEERING

GLP-1 dimer

Exendin-4

Lixisenatide

Liraglutide

97% homology to GLP-1

Ex-4 plus poly Lys

Albiglutide

Once Weekly Injection

Semaglutide

IgG Fc fragment

Dulaglutide

Two GLP-1s on Fc fragment

Once Daily Injection

Once Weekly Injection

Twice Daily Injection

Once Daily Injection

Once Daily Injection

Once Weekly Injection
Liraglutide and Semaglutide

- Lipidated GLP-1 analogues based on Novo lipidation system
- Liraglutide is 97% homologous to GLP-1
- Albumin binding by lipid for half-life extension
- Semaglutide has an optimized albumin binding side chain

Liraglutide
Approved EU 2009 / US 2010
Daily SC injection
1.2 to 1.8 mg per dose

Semaglutide
NDA 2016
Weekly SC Injection
1-2 mg per dose

1 mg at steady state
**EXENATIDE MICROSPHERE (BYDUREON) LIFE CYCLE**

- Bydureon is an exenatide microsphere formulation
- Vial and syringe, pen, suspension in auto-injector
- MS injectable suspension to be submitted by AZ 2017-2018?

<table>
<thead>
<tr>
<th>Product</th>
<th>Approval Status</th>
<th>Dosage Form</th>
<th>Dosage</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bydureon</td>
<td>Approved EU 2011 US 2012</td>
<td>Once weekly SC injection</td>
<td>2 mg per week dose</td>
<td></td>
</tr>
<tr>
<td>Bydureon Pen</td>
<td>Approved US 2014</td>
<td>Once weekly SC injection</td>
<td>2 mg per week dose</td>
<td></td>
</tr>
<tr>
<td>Bydureon Suspension</td>
<td>Anticipated Approval US 2018</td>
<td>Once weekly SC injection</td>
<td>2 mg per week dose</td>
<td></td>
</tr>
</tbody>
</table>

- Vial and syringe presentation discontinued Jan 2016 with pen launch

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PLGA Microsphere Dissolution Profile

Exenatide Weekly PLGA Microspheres (SEM)
Exenatide MS Release and Polymer Degradation

Exenatide MS Particle Size Distribution
BYDUREON: SINGLE DOSE PK PROFILE (10 TO 12 WEEKS)

Dose and Regimen Selection Study 2.5 mg, 6 mg, 7 mg, 10 mg

Initial release subject of significant formulation process work
And much discussion on clinical development strategy – is monthly achievable?
300 pg/ml continuous exposure desired – initial release too high
BYDUREON: MULTIPLE DOSE PK PROFILE

Dose Selection Study 0.8 mg and 2 mg exenatide
EXENATIDE LIFE CYCLE OPTIONS - PRODUCT HANDLING

Byetta solution 30 day pen
30 day RT in-use period
29 to 31 gauge needle

Both vial and syringe and dual-chamber pen
Require significant mixing prior to injection
25 gauge needle
**NEEDLE SIZE (LENGTH AND GAUGE) COMPARISON**

A

- **Volume (%)**
- **Particle Diameter (µm)**

<table>
<thead>
<tr>
<th>Needle Gauge</th>
<th>Inner Diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>0.260 mm</td>
</tr>
<tr>
<td>27</td>
<td>0.210 mm</td>
</tr>
<tr>
<td>30</td>
<td>0.159 mm</td>
</tr>
</tbody>
</table>

B

- **Regular standard sizes for general use**
- **For oils, serums, aspirating, etc.**

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EXENATIDE MICROSPHERE CONSIDERATIONS

- Formulation selection requires great care and lots of work
- Rodents were used for formulation screening
  - Good for initial release, duration not reflective of humans
- Minipigs a great model for human skin
- Scale up challenges are significant
  - Bench scale batches at 0.5 to 1 gram for formulation selection
  - Initial scale up from 1 to 100 gram in pilot equipment
  - Further scale up at 1 kg to 5 kg to 10 kg (large batches with lots of drug)
  - Reevaluation of PK at each step
- Most clinical work completed at 100 g to 500 g batch size
- Product presentation issues more significant than anticipated
- Suspension project a significant improvement
Integration of molecular properties, formulation, and device is key to achieving the desired product profile

Product use and self-administration drive device configuration, formulation design, molecular properties
Integration of molecular properties, formulation, and device is key to achieving the desired product profile.

Product use and self-administration drive device configuration, formulation design, molecular properties.

THANK YOU

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