Nasal Delivery of Biologics – case studies from Critical Pharmaceuticals

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Outline

• Advantages of nasal drug delivery
• Anatomy and physiology of the nasal cavity
• Challenges faced with nasal delivery of biologics
• CriticalSorb
• Examples of CriticalSorb with insulin and PTH
• Development of a hGH nasal formulation
Advantages of Nasal Drug Delivery

• 30% of new drugs are biologics
  – 98% given by injection
  – Patients strongly dislike injection
• Nasal drug delivery provides an attractive alternative
  – Large surface area
  – Excellent blood supply
  – Rapid onset of action
  – Avoids first pass metabolism
  – Ease of use and compliance
  – Potential for delivery direct to the brain and CNS
Challenges with Nasal Delivery of Biologics

- Absorption of macromolecules is poor:
  - Absorption promoting excipients are required
  - Tolerability of absorption enhancers
- Clearance from the nasal cavity via nasopharynx into the stomach
- Pharmacokinetic variability?
- Effect of nasal pathology?:
  - Increased mucus secretion
  - Mucociliary clearance rate
Absorption promoters for Nasal Delivery

• A number of absorption promoters have been developed and tested.
  – Many only provide small increase in bioavailability of biologics
  – Many suffer from tolerability issues

• For safe and effective delivery of biologics new absorption enhancers are required

• Critical Pharmaceuticals have developed CriticalSorb™ for transmucosal delivery of drugs
  – Shown to be safe and effective in nonclinical and clinical studies
CriticalSorb™ Delivery System

- Principle components are PEG mono- and diesters of 12-hydroxystearate
- Acts as a solubility and permeability enhancer.
- Used in marketed products for I.V. and oral administration.
  - Generally regarded as safe (GRAS)
  - Drug Master File in EU, USA and Japan
  - Extensive toxicology package
  - Non-toxic and non-irritant
- Well tolerated by the nasal mucosa in acute, 14 day and 6 month repeated dose chronic toxicity studies
- Shown in man to enable the nasal delivery of biologics.
Nasal Absorption Promoters

Often a link between damage to the mucosa and increase in bioavailability
CriticalSorb™ - best in class delivery technology
CriticalSorb™ Intranasal Insulin (rat)

In rats, CriticalSorb intranasal insulin has similar PK and PD profile to s.c. injection over 1h

**Pharmacokinetics**

<table>
<thead>
<tr>
<th>Time (mins)</th>
<th>Plasma Insulin (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>40</td>
<td>200</td>
</tr>
<tr>
<td>60</td>
<td>300</td>
</tr>
</tbody>
</table>

**F₀-₁h ~ 100%**

**Reduction in Blood Glucose**

- **Chitosan**
- **Control**
- **CriticalSorb Intranasal**
- **s.c.**

Same dose (4 IU/kg insulin)
Conscious rat model
Development of a nasal formulation for the treatment of osteoporosis

- Osteoporosis is a prevalent disease (40% women aged 80) characterised by low bone density and increased risk of fracture at an annual cost to the NHS of >£2bn
- Recombinant human Parathyroid hormone (PTH1-34) is currently the only anabolic therapy approved for the treatment of Osteoporosis
  - Forsteo® delivered by daily injection for two years
- This peptide is unique in its bone building capabilities, to promote bone strength and the ability to reduce long term bone fracture risk
- Critical Pharmaceuticals are developing a nasal formulation to replace daily injections
  - Phase 1 clinical trial in Q2 2013
  - Potential for improved efficacy over injectables
CriticalSorb™ Intranasal Parathyroid Hormone (rat)

I.N. bioavailability ~ 79%
S.C. Dose – 80µg/kg
I.N. Dose – 100 µg/kg
CP024: Intranasal hGH for Paediatric and Adult GH Deficiency
Why was CP024 developed

• Non-adherence to hGH therapy is as high as 66%\(^1,3\)
  – Non-adherence reduces efficacy
  – Increases healthcare costs

• Daily injections are strongly disliked\(^2\)
  • 70% of children and their carers do not like having to inject hGH on a daily basis
  • 30% of children injecting hGH on a daily basis are considering stopping their treatment because of the injection

• Nasal delivery is an attractive alternative
  • Children prefer nasal administration over injections\(^4\)
  • Improved adherence, convenience and ease of use

3: Cutfield et al, PLoS One (2011) 1;6(1) e16223
4: Flood et al, Vaccine 29 (2011) 4334-4340
CP024 Target Product Profile

• CP024 is being developed as an intranasal dry powder formulation of GH
  – Containing CriticalSorb™ absorption promoter
• Developed for the treatment of GH deficiency in children and adults
  – Efficacy and IGF-1 response equivalent to sc injection
• Safe and well tolerated in preclinical and phase 1 clinical studies
  – Similar safety profile to marketed nasal products (e.g. Beconase)
  – No injection site reactions
• Delivered by intranasal administration
  – Ease of use/no device preparation
  – A single or multi-dose nasal spray device and a range of dose levels
• Convenience
  – Stable at room temperature for >1 month, estimated shelf life >2 years at -20°C
Phase 1 Clinical Development

**Phase 1A**
- Five way cross over study in 8 healthy volunteers on octreotide
- Assess the tolerability, PK and PD (IGF-1 induction) of 2 prototype nasal formulations of GH and CriticalSorb

**Phase 1B**
- Three way cross over study in 7 healthy volunteers on octreotide
- Assess the tolerability, PK and PD (IGF-1 induction) of 6 doses of CP024

Nasal delivery using Aptar Pharma UDS Powder device
CP024 is Safe and Well Tolerated

- Tolerability similar to marketed nasal products (e.g. Beconase)
- AEs are mild and transient, no SAEs and no withdrawals
- No correlation with dose or powder mass

<table>
<thead>
<tr>
<th></th>
<th>Phase 1a</th>
<th>Phase 1b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinorrhea</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Sensation of pressure in the nose</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Sinus pain</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Blocked nose</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Sneezing</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Itching, red eyes</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Burning in sinus area</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Burning sensation in nostril</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total AEs</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Number nasal powder doses</td>
<td>32</td>
<td>52</td>
</tr>
</tbody>
</table>

- Tolerability similar to marketed nasal products (e.g. Beconase)
- AEs are mild and transient, no SAEs and no withdrawals
- No correlation with dose or powder mass
CP024 Pharmacokinetics vs. Omnitrope®

- Nasal no more variable than subcutaneous
- CP024 pharmacokinetics highly reproducible

Coefficients of Variation (Cmax)
- Omnitrope: 55.1%
- CP024: 52.8%

Relative Bioavailability
- CP024 vs Omnitrope
  - $F_{(0-2)}$: 16%
  - $F_{(0-last)}$: 3%

N=8 Error bars=SEM
IGF-1 Strongly Induced by CP024 B.D.

- CP024 twice daily strongly induces IGF-1 up to at least 19h
- CP024 is the first intranasal hGH demonstrated to induce IGF-1

**Graph:**
- Significant induction of IGF-1 up to 19h post-dose (p < 0.002)
- No significant difference between IGF-1 induction after intranasal CP024 b.d. and sc Omnitope

**Legend:**
- N = 8
- Error bars = SEM
CP024 is the First Intranasal GH to Induce IGF-1

- Previous clinical studies on intranasal GH failed to show any IGF-1 response
  1-5
  - Six studies reported in the literature
  - Formulations were poorly tolerated with frequent reports of pain, itching, burning, stinging and unpleasant taste
  - Poor tolerability was probably due to the absorption enhancers used (STDHF, DPPC, HPMC and α-cyclodextrin)

CP024 and the GH/IGF-1 Axis

- CP024 induces IGF-1 to a similar extent as an S.C. injection
  - Important for growth in children
  - Pulsatile PK profile may be important
    - Similar to profile after intranasal delivery
- Direct effects of GH not all positive
  - Increase insulin resistance
  - Conflicting reports on increased incidence of type 2 diabetes \(^1,^2\)
  - CP024 has lower systemic GH exposure

Summary

• Pharmacokinetics from nasal administration is no more variable than subcutaneous injection
• Intranasal delivery of biologics has to date been limited by:
  – Poor absorption
  – Poor tolerability of absorption enhancers
• A new generation of absorption enhancers have been developed:
  – Greater absorption
  – Better tolerated
• CriticalSorb has been shown to be a highly effective absorption promoter
  – Using CriticalSorb, CP024 is the first intranasal hGH to induce IGF-1 in man
  – CriticalSorb will be used to develop a nasal formulation of PTH
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