Oral Peptide Delivery: Successful Technologies Progressing in the Clinic and Future Challenges

J. Richard, PhD
Peptides Development
PEPTIDE DELIVERY LANDSCAPE
Most of the marketed peptides are injectable.
# Peptide Delivery: Technology Landscape

<table>
<thead>
<tr>
<th>Product</th>
<th>Peptide</th>
<th>Indication(s)</th>
<th>First approval</th>
<th>Sales (2013, US $Billion)</th>
<th>Route</th>
<th>Needle gauge</th>
<th>Dose volume (ml)</th>
<th>Dosing schedule</th>
<th>Drug delivery technology</th>
<th>Manufacturing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copaxone®</td>
<td>Glatiramer acetate</td>
<td>Multiple sclerosis</td>
<td>1996</td>
<td>4.3</td>
<td>s.c.</td>
<td>29G</td>
<td>1</td>
<td>Immediate release</td>
<td>–</td>
<td>Solution</td>
</tr>
<tr>
<td>Lupron® Depot</td>
<td>Leuprolide</td>
<td>Prostate cancer</td>
<td>1989</td>
<td>2.0</td>
<td>i.m.</td>
<td>22G</td>
<td>1</td>
<td>1, 3, 4, 6 month SR</td>
<td>PLGA microparticles</td>
<td>Emulsion/solvent extraction</td>
</tr>
<tr>
<td>Velcade®</td>
<td>Bortezomib</td>
<td>Myeloma</td>
<td>2003</td>
<td>1.7</td>
<td>s.c./i.v</td>
<td>n.s.</td>
<td>1 – 3.5</td>
<td>Immediate release</td>
<td>–</td>
<td>Lyophilization</td>
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<tr>
<td>Sandostatin® LAR</td>
<td>Octreotide</td>
<td>Acromegaly cancer</td>
<td>1998</td>
<td>1.6</td>
<td>I.m.</td>
<td>19G</td>
<td>2</td>
<td>Monthly release</td>
<td>PLGA glucose star polymer</td>
<td>Coacervation</td>
</tr>
<tr>
<td>Zoladex®</td>
<td>Goserein</td>
<td>Prostate cancer</td>
<td>1996</td>
<td>1.0</td>
<td>s.c.</td>
<td>14G</td>
<td>N/A</td>
<td>1 and 3 month SR</td>
<td>PLGA implant</td>
<td>Melt extrusion</td>
</tr>
<tr>
<td>Byetta® / Bydureon®</td>
<td>Exenatide</td>
<td>Diabetes</td>
<td>2005¹</td>
<td>0.5</td>
<td>s.c.</td>
<td>31G¹</td>
<td>0.04¹</td>
<td>Twice daily</td>
<td>PLGA microparticles</td>
<td>Solution¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2011¹</td>
<td></td>
<td></td>
<td>23G¹</td>
<td>0.65¹</td>
<td></td>
<td></td>
<td>Coacervation¹</td>
</tr>
<tr>
<td>Decapeptyl®</td>
<td>Triptorelin</td>
<td>Prostate cancer</td>
<td>1986</td>
<td>0.3</td>
<td>s.c./l.m.</td>
<td>21G</td>
<td>1.5</td>
<td>Immediate release and 1, 3, 4, 6 month SR</td>
<td>Lyophilize PLGA microparticles</td>
<td>Coacervation, lyophilization, melt extrusion and insoluble salts</td>
</tr>
<tr>
<td>Somatuline® Autogel®</td>
<td>Lanreotide</td>
<td>Acromegaly cancer</td>
<td>2001</td>
<td>0.25</td>
<td>s.c.</td>
<td>18G</td>
<td>1 month SR</td>
<td></td>
<td>Nanotubes</td>
<td>Peptide self-assembly</td>
</tr>
<tr>
<td>Eligard®</td>
<td>Leuprolide</td>
<td>Prostate cancer</td>
<td>2002</td>
<td>0.25¹</td>
<td>s.c.</td>
<td>19–20G</td>
<td>0.25–0.5</td>
<td>1, 3, 4, 6 month SR</td>
<td>In situ solidifying PLGA depot</td>
<td>N-methylpyrrolidone/PLGA injection vehicle mixed immediately prior to administration</td>
</tr>
<tr>
<td>Supprelin® LA</td>
<td>Histrelin</td>
<td>Precocious puberty</td>
<td>2007</td>
<td>0.06</td>
<td>s.c.</td>
<td>N/A</td>
<td>N/A</td>
<td>2 month SR</td>
<td>Nonbiodegradable implant</td>
<td>3.5cm x 3 mm cylindrical polymeric capsule</td>
</tr>
<tr>
<td>Suprefact®</td>
<td>Buserelin</td>
<td>Endometriosis, IVF</td>
<td>1990</td>
<td>N/A</td>
<td>Nasal</td>
<td>N/A</td>
<td>N/A</td>
<td>tds</td>
<td>Nasal spray</td>
<td>Solution</td>
</tr>
<tr>
<td>Synarel®</td>
<td>Nafarelin</td>
<td>Endometriosis, IVF</td>
<td>1990</td>
<td>N/A</td>
<td>Nasal</td>
<td>N/A</td>
<td>N/A</td>
<td>bd</td>
<td>Nasal spray</td>
<td>Solution</td>
</tr>
</tbody>
</table>
Peptide Delivery: Technology Trends

- **Injectable Sustained Release**
  - Current standard for peptide formulations: 1M to 6M
  - Various technologies available (microspheres, implants, self-assembly technologies, . . .)
  - Ready-to-use formulations in pre-filled syringes
  - Narrow gauge needles

- **Transdermal Peptide Delivery**
  - Proof of technology on-going for many technologies
  - Positive clinical Phase II results reported for micro-needle technologies (3M, Zosano, Nanopass . . .)

- **Oral Peptide Delivery**
  - A broad range of technologies
  - Numerous technologies now **validated clinically** in late stage trials (Phase II and III)
  - Octreolin filing of 505(b)(2) dossier by Chiasma in the US (Mycapssa™)
  - Strong competitive pressure

- **Intracellular Peptide Delivery**
  - Targeting of cancer cells for new oncology drugs
  - Brain targeting
FOCUS ON ORAL PEPTIDE DELIVERY
Oral Peptide Delivery: Strong Expectations from the Market

- Unmet medical need
- Delivery to site of action
- Competitive environment
- Late stage of development

**If approved, octreotide capsules would be the first and only oral somatostatin analog, providing another option to patients currently receiving painful injections.**

**Oral Linaclotide – Targeting Receptors in the GI Tract**

J. Castro et al, Gastroenterology, 145(6), 2013, 1334-1346

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**FierceBiotech**

Chiasma hauls in $70M to write future

Chiasma announces FDA Acceptance for Filing of New Drug Application for Octreotide Capsules in Acromegaly

*Brand name of Mycaprog* is also conditionally accepted by agency.

NEWTON, Mass. and JERUSALEM, Israel, Aug. 17, 2015 /PRNewswire/ -- Chiasma, Inc. (Nasdaq: CHMS) today announced that the U.S. Food and Drug Administration (FDA) has accepted for review its New Drug Application (NDA) for octreotide capsules. The NDA is for the use of octreotide capsules to treat acromegaly, a rare, chronically debilitating condition associated with the overgrowth of bones and tissues due to excessive growth hormone production.

With the money in hand, Chiasma will advance its pipeline of treatments for the condition.

An oral long-acting somatostatin analog, providing another option to patients currently receiving painful injections. Chiasma is committed to developing an oral formulation of octreotide, a somatostatin receptor agonist that has been approved in Europe for over 30 years.

**Drug delivery tech helps novel biotech**

Emisphere Signs License Agreement With Novo Nordisk to Develop Oral Formulations of Four Molecules Targeting Metabolic Indications and Amends CGL-1 Agreement


Emisphere Technologies, Inc. (Emisphere) and Novo Nordisk A/S (Novo Nordisk) announced today that the companies have signed a license agreement to develop oral formulations of four molecules targeting metabolic indications. Emisphere is eligible to receive an upfront payment of $14 million from Novo Nordisk, as well as milestone payments, and royalties on sales of products resulting from the agreement.
**Marketed Oral Peptides**

- Most are used **for local action** in the gastrointestinal tract (not absorbed systemically)
- Striking number of **cyclic** peptides – resistance to exopeptidases
- Those that are systemically absorbed are important as they **demonstrate financial viability** and efficacy are possible even with low and variable bioavailability

<table>
<thead>
<tr>
<th>Product</th>
<th>Indication</th>
<th>Peptide</th>
<th>Mw (g/mole)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colomycin®</td>
<td>Infection</td>
<td>colistin sulfate</td>
<td>1268</td>
<td>Cyclic peptide</td>
</tr>
<tr>
<td>Neoral®</td>
<td>Immunosuppression</td>
<td>cyclosporine</td>
<td>1202</td>
<td>Cyclic peptide, practically insoluble in water</td>
</tr>
<tr>
<td>Sandimmune</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minrin®</td>
<td>Nocturia</td>
<td>desmopressin acetate hydrate</td>
<td>1183</td>
<td>Soluble salt of cyclic peptide. F = 5% compared to intranasal DDAVP, and about 0.16% absolute bioavailability. Sublingual (melt) formulation achieves 0.25%</td>
</tr>
<tr>
<td>Minrin® Melt</td>
<td>Diabetes insipidus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cachexon®</td>
<td>AIDS-related cachexia</td>
<td>glutathione</td>
<td>307</td>
<td>Tripeptide also found in a number of health supplements</td>
</tr>
<tr>
<td>Linzess®</td>
<td>Irritable bowel syndrome, constipation</td>
<td>linaclotide</td>
<td>1527</td>
<td>Cyclic peptide agonist of guanylate cyclase 2C derived from E.Coli enterotoxin</td>
</tr>
<tr>
<td>Ceredist®</td>
<td>Spinocerebellar ataxia</td>
<td>taltirelin hydrate</td>
<td>477</td>
<td>Practically insoluble Thyrotropin Releasing Hormone (TRH) analogue. <strong>Centrally acting.</strong></td>
</tr>
<tr>
<td>Ceredist OD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiovag®</td>
<td>Pharyngitis</td>
<td>tyrothricin</td>
<td>1228</td>
<td>Cyclic polypeptide, practically insoluble</td>
</tr>
<tr>
<td>Vancocin®</td>
<td>Infection</td>
<td>vancomycin hydrochloride</td>
<td>1485</td>
<td>Tricyclic glycopeptide antibiotic, freely soluble</td>
</tr>
</tbody>
</table>

Source: Pharmacircle Database
Main Challenge: Peptides Are Poorly Absorbable Through the GI Tract, Whatever the Transport Mechanism

- To increase absorption, need for permeation enhancers:
  - Novel excipients
  - Nanoparticle approaches

- Opportunity to target receptors in the GI tract:
  - Local treatment of GI disorders (e.g. IBS)
  - Triggering a signal transduction cascade

Intestinal epithelial monolayer stained for the tight junction protein ZO-1. Note surface area differences: transcellular vs paracellular routes.
Examples of oral technologies progressed into the clinics
- Formation of lipophilic transportable complex by weak non-covalent interactions with a carrier
- Formation of crystals (specific of particular APIs)
- Formation of calcium phosphate (CAP) nanoparticles (e.g. CAP-PEG-insulin-casein nanoparticles)
- Formation of micellar solutions for buccal delivery (e.g. Oral-Lyn™, commercialized in India)
- Formation of amphiphilic oligomers by modification with lipophilic moieties to enhance transcellular absorption and peptide stability (e.g. hexyl-insulin monoconjugate 2, HIM2 commercialized as Insugen™ in India)
Technological Approaches

- Absorption enhancers
  - Acylcarnitine
  - Bile salts
  - Fatty acids and their derivatives
  - Acylated amino acids e.g. SNAC, 5-CNAC
  - Salts of EDTA
  - Hydrophilic aromatic alcohols
  - Alkylsaccharides
  - Bacterial toxin conjugates
  - Cell penetrating peptides
  - PEG and glycolipid conjugates

Most commonly investigated and successful approach

- Enzymes inhibitors
  - Inorganic acids e.g. citric acid
  - Soy bean trypsin inhibitor
  - SEDDS systems
  - Aprotinin

- Mucoadhesive systems
  - Chitosan and derivatives
  - Polymeric

- Conjugates
  - Bacterial toxin conjugates
  - Cell penetrating peptides
  - PEG and glycolipid conjugates

- Functionalized Nanoparticles

Pridgen et al., 2013
Merrion Technology - GIPET (I, II, III)
Gastro-Intestinal Permeation Enhancement Technology

- Medium chain fatty acids and their salts – sodium caprylate, sodium caprate and sodium laurate
- Absorption enhancer is blended with API and formulated into enteric coated tablet

Clinical Stage
- Phase II for oral zolendronic acid
- Phase I for oral insulin (with NovoNordisk)
- Phase I for oral GLP-1

Merrion Pharma to sell assets to Novo Nordisk
Merrion will use the proceeds to pay off $5m loan from Irelandia Investments

Merrion to develop oral GLP-1 drug for Novo
Ireland’s Merrion Pharmaceuticals’ GIPET oral delivery technology platform has won the firm its second licensing agreement with Danish insulin giant Novo Nordisk.

The deal, which could earn Merrion up to $58m, will see the firm develop an oral formulation of Novo’s GLP-1 receptor antagonist candidate, extending the initial agreement the two companies signed in November.
Enteris Biopharma – Technology Peptelligence

- Completed numerous clinical studies
  - Phase III for oral Calcitonin: Osteoporosis – demonstrated increased efficacy vs nasal spray
  - Phase II for oral PTH: Osteoporosis – increased bone density but not as much as injection
  - Phase II for oral Calcitonin: Osteopenia
  - Phase I for oral CR845: Neuropathic Pain
- Paternerships with Tarsa, Cara Therapeutics and Nordic Bioscience
- Enteris has full development and clinical manufacturing and testing capabilities for the technology
**Fc-Targeted Nanoparticles (NPs) For Oral Peptide Delivery**

NP assembly, functionalization, and *in vitro* transepithelial transport

DPM = basolateral $^3$H disintegrations per minute, as a percentage of the initial amount of $^3$H. An excess of human IgG Fc is used as a blocking agent for FcRn.

**Transepithelial Transport by the Neonatal Fc Receptor (FcRn)**

Schematic of Fc-targeted NP active transportation mechanism across the intestinal epithelium by the FcRn through a transcytosis pathway.

Fc-Targeted Nanoparticles: Absorption and Biodistribution in Mice

Fig. 4. NP absorption and biodistribution in mice. (A) Biodistribution of $^{14}$C-labeled nontargeted NPs and NP-Fc after oral administration to fasted WT mice. Data are mean percent initial dose (%ID) per gram of tissue ± SEM (n = 5 mice per time point). (B) Release of $^{14}$C from $^{14}$C-labeled NPs in PBS at 37°C. Data are means ± SD for n = 4 release experiments. (C) Total absorbed $^{14}$C over time for nontargeted NPs and NP-Fc after administration by oral gavage. Data are mean %ID measured in all of the organs added together ± SEM (n = 5 mice per time point). **P < 0.01 for comparison of nontargeted NPs and NP-Fc at respective time point, two-tailed Student's t test.

Oral absorption of NP-Fc is strongly enhanced in mice vs non targeted NPs

<table>
<thead>
<tr>
<th>Company</th>
<th>API</th>
<th>Technology name</th>
<th>Technology</th>
<th>Stage of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiasma</td>
<td>Octreotide</td>
<td>TPE</td>
<td>Enteric coated liquid filled capsules containing a <strong>suspension of drug particles in oils</strong></td>
<td>Filing</td>
</tr>
<tr>
<td>Enteris Biopharma</td>
<td>Calcitonin</td>
<td>Peptelligence</td>
<td>Enteric coated capsule containing peptide with <strong>absorption enhancer (acyl carnitine)</strong> and <strong>enzyme inhibitor (organic acid)</strong></td>
<td>Phase III</td>
</tr>
<tr>
<td>Nobex/Biocon</td>
<td>Insulin conjugate</td>
<td>HIM2</td>
<td>Peptide amphiphilic <strong>conjugate pro-drug</strong> technology in which the peptide is covalently linked to PEG, glycolipids or fatty acids and formulated with <strong>absorption enhancers</strong></td>
<td>Phase III</td>
</tr>
<tr>
<td>Oramed</td>
<td>Insulin and exenatide</td>
<td>POD</td>
<td>Peptide with <strong>absorption enhancer</strong> and enzyme <strong>inhibitors</strong> in enteric coated tablet/capsule</td>
<td>Phase II</td>
</tr>
<tr>
<td>Emisphere</td>
<td>GLP-1 analogue</td>
<td>Eligen</td>
<td>Tablet formulation based on <strong>absorption enhancers</strong> SNAC, SNAD, 5-CNAC</td>
<td>Phase II</td>
</tr>
<tr>
<td>Merrion</td>
<td>Insulin and GLP-1</td>
<td>GIPET</td>
<td>Enteric coated tablets containing <strong>medium chain fatty acids</strong> (sodium caprate) as an <strong>absorption enhancer</strong></td>
<td>Phase I</td>
</tr>
<tr>
<td>MidaTech</td>
<td>Insulin and GLP-1</td>
<td>GNP / Nanocells</td>
<td>Surface modified <strong>gold nanoparticles</strong> complexed with peptides and formulated into <strong>adhesive buccal</strong> patch</td>
<td>Phase I</td>
</tr>
<tr>
<td>Nod Pharma</td>
<td>Insulin and GLP-1</td>
<td>NOD</td>
<td><strong>Calcium nanoparticles</strong> in <strong>mucoadhesive</strong> tablet formulation</td>
<td>Phase I</td>
</tr>
</tbody>
</table>
Intra-Enteral Injection Using “Robotic Pills”: A Paradigm Shift

Can ‘Robotic’ Pills Replace Injections?
Entrepreneur Mir Imran Hopes to Change Diabetes Treatment

Figure 2: Sr Delivery of “robotic pill” concept comprising a capsule containing a valve, and an inflatable balloon-like structure with chemical compartments composed of citric acid and sodium carbonate, and is dissolved by the pill coating sugar and preloaded with the therapeutic peptide.

AstraZeneca funds ‘robotic pill’ company Rani Therapeutics in pursuit of oral biologics

Novartis AG has an extensive line of biologic drugs that can only be taken by injection, but now the pharmaceutical giant is making a bet on a “robotic pill,” a peroral product that could make drugs like insulin available for the first time without the use of a needle.

Novo Nordisk and MIT on the hunt for oral peptide route

If the project to develop a successful peptide drug delivery system from pills to pill form
LESSONS LEARNT FROM CLINICAL STUDIES: 
ADDRESSING THE CHALLENGES OF PEPTIDE STABILITY IN THE GI TRACT AND ORAL BIOAVAILABILITY
Achieving Similar Pharmacokinetics to S.C. Injection

- Chiasma Octreolin Phase I data (4 studies & 75 patients)
  - PK (12 males), dose escalation vs s.c
  - Food effects (11 females / 13 males)
  - PK/PD (13 females / 11 males)
  - Duration of intestinal permeability
  - Effect of proton pump inhibitor

**FIG. 3.** Comparable plasma octreotide concentrations after oral or sc injection of octreotide acetate. Mean plasma concentrations of octreotide after a single oral administration of 20 mg octreotide acetate (closed diamonds, n = 24; closed squares, n = 12; closed circles, n = 17) and single sc injection of 0.1 mg octreotide acetate (closed squares, dotted line; n = 14) to healthy volunteers.

*Tuvia et al, JCEM, 97(7) 2362-2369, 2012*

- 20 mg oral Octreotide achieved similar PK parameters to 0.1 mg subcutaneous injection
- Food and PPIs decreased bioavailability (90% and 40% respectively)
Orally-Delivered Peptide Remains Bioactive

Orally Delivered Octreotide is Bioactive

Data are presented as Mean ± SE, N=18

GHRH-Arg = growth hormone-releasing hormone + arginine.

Tuvia et al, J Clin Endocrinol Metab, 97(7), 2362-2369, 2012
Increased Efficacy from Oral Peptide Delivery

- Tarsa Therapeutics / Unigene labs technology Phase III on oral calcitonin
  - 565 post-menopausal women with documented osteoporosis
  - 0.2mg sCT orally vs placebo and marketed nasal spray (33µg sCT)
  - Note: formulation did not contain acyl carnitine

- Safe and well tolerated
- Greater increase in lumbar spine bone mineral density (LS-BMD)
- FDA and EMA subsequently advised against use of calcitonin in osteoporosis

Binkley et al, JMBR 27 (8), 1821-1829, 2012
Potential Unexpected Food Effects

- Nordic Biosciences / Emisphere oral calcitonin
  - 40 post-menopausal healthy volunteers
  - 0.8mg calcitonin orally
  - Effect of 50mL vs 200mL water
  - Effect of dosing time before meal

- Bioavailability 4x greater than nasal calcitonin

$C_{\text{max}}$ increased 2 – 3x when taken with 50mL water vs 200mL

Bioavailability increased with increasing time before the meal

Karsdal et al, BMC Clinical Pharmacology, 2008
FUTURE CHALLENGES
Anticipating the Switch From Injection to the Oral Route

- Relative bioavailabilities are expected to remain quite low (< 5%), even for smallest peptide in state of the art technologies

- Dosing frequency may need to increase (i.e. once daily s.c. to twice daily oral) – Impact on attractiveness of oral treatment vs injections every 3M or 6M

- The anticipated CoGs (at least for the API) are therefore likely to be high, however:
  - No need for aseptic manufacturing (cheaper to manufacture the drug product)
  - Cost of API decreases as production scale increases
  - Would the switch bring an upside in sales?

- The impact on API demands needs to be considered:
  - May require significant investment in new facility and high yield synthesis processes

- Will a (more expensive?) oral treatment be reimbursed?
  - Demonstrate superiority vs reference treatment?
  - Increased safety or efficacy?
## Bioavailability and Competing Technologies

<table>
<thead>
<tr>
<th>Route of Delivery</th>
<th>Technology</th>
<th>Companies</th>
<th>Most Advanced Stage of Development</th>
<th>Highest Relative Bioavailability (v.s. s.c.) Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transdermal</td>
<td>Microneedles</td>
<td>Nanopass</td>
<td>Phase III (vaccines)</td>
<td>Dose sparing effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zosano</td>
<td>Phase II (PTH)</td>
<td>40% PTH in man, increased efficacy(^1), RT stable 2 years</td>
</tr>
<tr>
<td>Nasal</td>
<td>Absorption Enhancers</td>
<td>Serenity Pharma</td>
<td>Phase III (vasopressin analogue)</td>
<td>Same technology achieved 20% for insulin in man(^2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Azelon</td>
<td>Phase II (PTH)</td>
<td>39% PTH in non-human primates(^3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Critical Pharma</td>
<td>Phase I (hGH)</td>
<td>20% hGH in non-human primates(^4)</td>
</tr>
<tr>
<td>Inhaled</td>
<td>Novel excipient</td>
<td>Mannkind Corporation</td>
<td>Received marketing authorisation (Insulin - Afrezza)</td>
<td>30% insulin in man(^5)</td>
</tr>
</tbody>
</table>

- The oral route offers the lowest bioavailability for peptide delivery compared to other alternative routes (transdermal, nasal, . . .)

5. FDA Briefing Document, Endocrinologic and Metabolic Drugs Advisory Committee Meeting, April 1, (2014)
Key Challenges: A Summary

- Food effects & DDI
  - Bioavailability decreased
    - 90% - Food
    - 40% - PPIs

- Bioavailability and variability vs other routes
  - Route of Delivery | Technology | Companies | Most Advanced Stage of Development | Highest Relative Bioavailability (v.s. s.c.) Reported
  - Transdermal | Microneedles | Nanopass | Phase 3 (vaccines) | Dose sparing effect
  - | | Zosano | Phase 2 (PTH) | 40% PTH in man, increased efficacy, RT stable 2 years
  - Nasal | Absorption Enhancers | Serenity Pharma | Phase 3 (vasopressin analogue) | Same technology achieved 20% for insulin in man
  - | | Azelon | Phase 2 (PTH) | 39% PTH in non-human primates
  - | | Critical Pharma | Phase 1 (hGH) | 20% hGH in non-human primates
  - Inhaled | Novel excipient | Mannkind Corporation | Received marketing authorisation (Insulin - Afrezza) | 30% insulin in man

- Peptide stabilization

- Absorption enhancers safety
CONCLUSIONS
Future Prospects for Oral Peptide Delivery

- Oral formulations of peptides are highly desirable:
  - Increase therapeutic options, with unmet needs more particularly in Oncology
  - Help patient adherence and convenience

- Technologies to enhance systemic bioavailability of orally administered peptides are now clinically proven:
  - Successfully completing Phase III and progressing to fast track filing
  - Enhanced efficacy
  - Demonstrated safety

- An oral peptide formulation soon on the market:
  - Chiasma’s oral formulation of octreotide, brand name MyCapssa™, with orphan drug status in the US and EU
  - Treatment of acromegaly in the US with a PDUFA expected in April 2016 (Chiasma Press release January 8, 2016)
  - EMA approval to initiate a Phase III trial in acromegaly for market authorization submission in Europe with EMA approval expected in 2019/2020
Future Prospects for Oral Peptide Delivery

- Numerous factors must be considered to identify good candidates for oral peptide delivery:
  - Bioavailability, food effects, CoGs, manufacturing strategy, market access, upside in sales
  - For this reason it is likely that peptides will continue to be mostly administered via the injectable route in the next years

- However, over the next 5 – 10 years, increasing number of peptides will likely be delivered via the oral route.

- What impact the success or failure of next oral peptides on the market (e.g. Mycapssa™) will have on development of oral peptide delivery technologies?
ACKNOWLEDGEMENTS

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THANK YOU

Questions?

References:

1 - Challenges in the delivery of peptide drugs: an industry perspective

2 – Oral peptide delivery: technology status landscape and current status