Development of an Active Transdermal System: Complexity of Parallel Development of Formulation, Device, Patch, and Manufacturing Systems
Outline

- Type II Diabetes Market 2000 to 2020
- Exenatide for Type II Diabetes
- Exenatide Line Extension Options (Amylin-Lilly)
- Altea Passport Patch
  - Formulation Development
  - Device Development
  - Patch Development
  - Manufacturing Systems Development
Diabetes Market 2005-6
Injectable Insulin / Orals

- Human insulin
- Animal insulin
- Sulfonylurea
- Glitazones
- Metformin
- DPP-4
- GLP-1 analogs
- Inhaled insulins


- Transdermal System Development

DDP 01/27/14
Byetta Launched 2005 by Amylin-Lilly Partnership
Diabetes Market
2006 to 2020

HbA1C Change
-0.9%
-0.7%
-1.2%
-0.7%
-1.5%

Byetta (exenatide) GLP-1
Januvia (DPPIV)
Janumet (DPPIV and metformin)
Victoza (liraglutide) GLP-1
Bydureon (exenatide MS) GLP-1
Invokan (canagliflozin) SGLT2
Farxiga (dapagliflozin) SGLT2
TBD (empagliflozin) SGLT2
albiglutide GLP-1
dulaglutide GLP-1

QW SC Inj
QD SC Inj
QD Oral
Monthly SC Inj
Q6Mos or Yrly Implant GLP1
Oral GLP1
INS-GLP1 combos

GLP-1s Move to Maximize Continuous Exposure

Exenatide (Byetta)

-0.9% HbA1C reduction

Liraglutide (Victoza)

-1.5% HbA1C reduction

Exenatide MS (Byrureon)


Kim D et al. Dia Care 2007;30:1487-1493
Competitive Product Profiles (Insulins, GLP-1s)

- Patient self-administered
  - Simple injection device for impaired patients

- Minimal handling
  - No or easy reconstitution
  - 30 day RT storage for daily pen (warehoused at 5C)
  - 24 hour storage at RT for weekly or monthly injection (warehoused at 5C)

- Subcutaneous injection

- Daily injection
  - 30 day pen containing cartridge and preserved solution (depends on PK)
  - 31 gauge needle

- Weekly or monthly
  - Disposable auto-injector with pre-filled syringe (no preservative)
  - No larger than a 27 gauge needle (prefer 30 gauge)
Is There A Role for Non-Invasive Exenatide?

- Non-invasive systems
  - Multiple Daily Oral, Nasal, Pulmonary
  - Potentially very large market by pushing product into earlier diabetes continuum (larger patient population, general practitioner)

- Transdermal System
  - Potential for extended exposure from a bandaid-like patch
  - ‘Non-invasive’ with continuous exposure efficacy
Non-Invasive Drug Delivery Systems

Nasal spray product
- Aqueous solution formulation
- Simple manufacturing process
- Commercially available device
- Nasal peptide products in market
- BID or TID administration

Pulmonary inhalation product
- Dry powder formulation
- Spray dry manufacturing process
- Alkermes or Nektar device
- Insulin products near market
- BID or TID administration
Nasal Exenatide Exposure in Humans

Plasma exenatide peaked at 15-30 min vs. 2 hours with SC
Exenatide Nasal Conclusions

- Formulations identified and tested in rodents and primates
- Two formulations tested in humans
- Human bioavailability low but not primary issue
- Variability in exposure too high at peak
- Byetta like efficacy was achievable with two to three nasal sprays per day
- Program was halted
Choice of Active Transdermal Program

- Altea had an attractive transdermal system
  - Electroporation system
- Phase 1 completed with insulin
- Opportunity to develop a 24 hour continuous patch
- Amylin and Lilly signed agreement with Altea
- Altea Passport Patch Development
  - Patch formulation needed for exenatide
  - Device design and development needed
  - Patch configuration development needed
  - Commercial manufacturing systems needed
- Lilly also had an active collaboration on PTH with Transpharma
  - No continuous exposure formulation
Development Risks Identified

- Exenatide 24 hour patch for once daily administration
  - Uncertain until formulation work complete
- Device and patch under development
  - Configuration sub-optimal and needed work to make it usable
- Manufacturing systems and suppliers under-developed
  - Patch and device supplier would need to be developed
  - Some new materials for pharmaceutical device-drug product
- Approvability uncertain
  - No product precedent approved, but, some in development
  - Safety related to immunogenicity (resolvable with phase 2b)
- Decision was made to proceed despite concerns
- Potential commercial value significant
  - Patch form of GLP-1 delivering Bydureon-like efficacy
Application Process for Altea Passport Patch

Place patch on charged device, expose filament

Apply against skin, Activate current for msec pulse, Remove device leaving patch

Fold formulation over pores leaving ‘bandaid’
Altea Prototype System

Electronic device:
Delivers inductive current to filament

Patch system:
Adhesives / layers house disposable filament and formulation / ‘bandaid’

Challenges
- Size of device / components
  - Patch application confusing
  - Pealing off multiple layers
  - Folding over formulation onto pores
- Multiple MFG partners and unique suppliers
- Regulatory risk of approval
Transdermal Program

- Develop exenatide polymer formulation
  - Optimize for continuous 24 hour exposure (designed for maximum efficacy)
  - Consider minimally acceptable 2X per day application

- Test in hairless rats for PK
  - Identify formulations and poration conditions
  - Optimize bioavailability and onset and duration of exposure

- Develop device
  - Reduce size and improve handling by patients
  - Develop manufacturing process and suppliers

- Develop patch
  - Improve handling and application process
  - Develop manufacturing process and suppliers

- Proof of feasibility
  - Test formulation in human PK study
Exenatide Transdermal Development Program

Formulation
- Initial PK Feasibility
  - Altea
- Optimize PK to Extend Exposure at Good BA
  - Monitor process integrity
  - Stability prototypes
- Human PK Study

Patch
- Identify Poration Intensity
  - Pore Density, Patch Size
  - Altea
- Optimize Patch Handling
  - Cambridge Consulting
- Identify Supply Partners
  - 3M, others

Device
- Minimize device size and improve patient handling
  - Ideo
- Identify Supply Partners
  - Device manufacturer
Parallel Development
Inter-related Uncertainties

- Formulation identity – Go No Go for proceeding
- Device and patch configuration – commercial implications for patient acceptance
- Manufacturing systems and suppliers – implications for COGs
- Integration challenge – moving parts have an impact on one another
- Importance of market timing – causes parallel development of formulation, device, patch
Figure 1. (Top) Exenatide released into PBS from extended-release transdermal film over 24 hours. (Bottom) Exenatide pharmacokinetics in the hairless rat after microporation and 24 h application of extended-release transdermal film.

Figure 2. (Top) Exenatide released into PBS from rapid-release transdermal film over 24 hours. (Bottom) Exenatide plasma in the hairless rat after microporation and 24 h application of rapid-release transdermal film.
New and Improved Altea Device and Patch System

Preclinical proof of concept

Device and patch optimized with IDEO for ease of handling by 55+ year old diabetic

Patch redesigned with Cambridge Consultants for simplified application

Manufacturing partners for supply chain identified (device, formulation / patch)
Exenatide Transdermal Conclusions

- Overall, the transdermal system for Exenatide performed well. 
- Drug delivery was consistent across different formulations.
- Patient compliance with the transdermal device was high.
- Further studies are needed to explore long-term efficacy and safety.
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