Adare Pharmaceuticals
A Patient-Centric Approach to Drug Formulation

Drug Delivery & Formulation Summit
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Director of Business Development

Luigi Boltri
Director, Innovation & Technology Liaison
Patients and our partners are at the heart of everything we do
We are a global specialty pharmaceutical company inspired to improve the lives of patients whose treatment needs are not fully addressed by current medications.
Corporate Overview

- Profitable, $150M revenues (2016)
- Product commercialization capabilities
- Unique pharmaceutical technologies
- Global Footprint
- Proven Leadership Team
- Actively seeking acquisitions in select markets
- Supported by TPG Capital
- Pipeline
  - 8 proprietary development assets
  - Current focus in CNS and GI
Global Locations

Established Commercial Operations in North America and Europe

Multinational Presence To Serve Global Markets

- Mont-Saint-Hilaire
- Princeton
- Vandalia
- Houdan
- Pessano
- San Giuliano
**Business Model**

| Product Portfolio | • Portfolio of 40 products commercialized through partners  
|                   | • Over 60 launches by our partners since 2009  
|                   | • Commercialization of selected pipeline products  
| Pipeline          | • Differentiated, high value products  
|                   | • Develop complex proprietary specialty and generic products addressing the unmet needs of patients  
| Formulation Development | • Co-develop new formulations in partnership with biotech/pharma companies  

Product Launches in Major and Emerging Markets

Since 2009, Over 60 Product Launches in 44 Countries

Over 40 Products incorporating our proprietary technologies have been commercialized around the world
Proprietary Pipeline

- 6 NDAs and 2 ANDAs
  - APT-5025 GUDFUA date: March 2017
  - APT-5031, a complex generic for CNS due to file with FDA in 2017
- Initial markets target for approval in US and Europe

Partnered products not disclosed
## Broad Proprietary Technology Portfolio

<table>
<thead>
<tr>
<th>Taste-masking and ODTs</th>
<th>Customized Drug Release</th>
<th>Bioavailability enhancement</th>
</tr>
</thead>
<tbody>
<tr>
<td>• AdvaTab®</td>
<td>• Diffucaps®</td>
<td>• Biorise™</td>
</tr>
<tr>
<td>• Microcaps®</td>
<td>• Diffutab®</td>
<td>• Diffucaps®</td>
</tr>
<tr>
<td>• Liquitard®</td>
<td>• MMTS™</td>
<td></td>
</tr>
<tr>
<td>• Orbexa™</td>
<td>• Orbexa™</td>
<td></td>
</tr>
</tbody>
</table>

- Eight distinct oral formulation technologies
  - Scaled-up and validated
  - Commercialized worldwide
  - Patent protected
- Applicable to Rx and OTC products — therapeutic area agnostic

Create patient-centric formulations:
- novel products and differentiation for line extensions
Track Record of Partnering Success

Over 40 Products Incorporating Our Proprietary Technologies Have Been Commercialized Around the World

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### Examples of Successful Drug Development

<table>
<thead>
<tr>
<th>Active</th>
<th>Company</th>
<th>Description</th>
<th>Technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrolide</td>
<td>Undisclosed</td>
<td><strong>Antibiotic formulated as dry syrup</strong> to ensure TM up to 5 days once suspended in water</td>
<td>Microcaps®, Diffucaps®</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Description</th>
<th>Technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zenpep</td>
<td>Allergan</td>
<td><strong>Pancreatic enzymes in delayed release capsules</strong> Reliable delivery through Gastrostomy Tubes</td>
<td>MMTS™</td>
</tr>
<tr>
<td>INNOPRAN XL</td>
<td>ani Pharmaceuticals, Inc.</td>
<td><strong>Propranolol HCl in customized release capsules</strong> FDA approved for treatment of hypertension</td>
<td>Diffucaps®</td>
</tr>
</tbody>
</table>

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Microcaps® Taste Masking Technology

CASE STUDY
Dry Syrup
Long Lasting - Taste Masking
Microcaps® - Complete and Effective Taste-masking

- Microencapsulation by coacervation:
  - Uniform coating of a solid particle or liquid droplet with a rigid semi-permeable polymer
- Creates a physical barrier:
  - Effective taste masking
  - Customized release profile
  - Turn liquids into solids
  - Combine incompatible APIs

Adare is a leader in organic phase coacervation for pharmaceutical products
Easy to Swallow

- Formulated as a direct dose sachet or ODT (to further improve patient compliance) makes it easy to swallow and support oral administration without need for liquid.
- The sachets can be opened and the contents used also as a "sprinkle" formulation.
# Case Study: Antibiotic Dry Syrup
Secure Long Lasting Taste Masking for Extemporary Suspension

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Antibiotic - Macrolide</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEED</td>
<td>Taste-mask a bitter API</td>
</tr>
<tr>
<td></td>
<td>Suitable to secure</td>
</tr>
<tr>
<td></td>
<td>✓ Fast release in gastric environment</td>
</tr>
<tr>
<td></td>
<td>✓ Reduced particle size for pediatric population</td>
</tr>
<tr>
<td></td>
<td>✓ At least 5 days taste-masking once suspended in water</td>
</tr>
<tr>
<td>SOLUTIONS</td>
<td>Oral powder formulation using Microcaps® taste masking</td>
</tr>
<tr>
<td></td>
<td>Commercial presentation: Dry Syrup suitable for reconstituting a suspension and administering a daily dose of 15/30 mg/kg</td>
</tr>
</tbody>
</table>
Double Coating: Taste-masking + pH Dependent

Pure API
PSD ≈ 100 µm

55 - 70% (w/w)

Primary Coating
Microcaps®

10 - 15% (w/w)

Secondary Coating
Diffucaps®

20 - 30% (w/w)

Double coating of single particles: original PSD practically preserved
Taste Masking Preserved for >10 Days in Suspension

- Taste masking prolonged by appropriate formulation of excipients (suitable buffer)

<table>
<thead>
<tr>
<th>Time</th>
<th>Microscope</th>
<th>TM evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start</td>
<td>membrane OK</td>
<td>tasteless</td>
</tr>
<tr>
<td>1 day</td>
<td>membrane OK</td>
<td>tasteless</td>
</tr>
<tr>
<td>4 days</td>
<td>membrane OK</td>
<td>tasteless</td>
</tr>
<tr>
<td>7 days</td>
<td>membrane OK</td>
<td>tasteless</td>
</tr>
<tr>
<td>11 days</td>
<td>membrane OK</td>
<td>tasteless</td>
</tr>
<tr>
<td>15 days</td>
<td>secondary coating</td>
<td>tasteless</td>
</tr>
<tr>
<td></td>
<td>partially swollen</td>
<td></td>
</tr>
</tbody>
</table>
Balance Taste Masking and Narrow Absorption Window

- Rapid release at gastric conditions demonstrated *in vitro* and *in vivo*
- Achieved bioequivalence in pilot clinical study (N=15)

**In vitro dissolution**

<table>
<thead>
<tr>
<th></th>
<th>DRT HCl 0.1N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2'</td>
<td>% Released</td>
</tr>
<tr>
<td>SD</td>
<td>4'</td>
</tr>
<tr>
<td>10'</td>
<td>SD</td>
</tr>
<tr>
<td>30'</td>
<td>SD</td>
</tr>
<tr>
<td>Prototype A</td>
<td>97</td>
</tr>
<tr>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>98</td>
<td>98</td>
</tr>
</tbody>
</table>

**Pilot clinical study (N=15)**

![Graph showing Double Coating Prototypes (A and B) vs Reference Product Healthy Volunteers – n=15](image)
Antibiotic Dry Syrup - Successful Development

• **10+ days taste masking** in extemporary suspension, while maintaining rapid release properties after administration

• **Final PSD well below 200 µm** to grant suspension homogeneity, minimize sandy effect and improve patient compliance (infants)

• **High drug load secured** (up to 70%), considering the small PSD (i.e. high surface area) of the starting material

• **Bioequivalence** proven in pilot clinical study
MMTS™  Multi Mini Tablet System
CASE STUDY
Deliver drugs through Gastrostomy tube
MMTS™ Multi Mini Tablet System

- **Combining tablet and multiparticulate** dosage form
  - High drug loading capacity
  - Titration of a broad dosage range
  - Wide range of customized release profiles in a single capsule
- **Improving ease of administration** for patients with swallowing difficulties
  - Broad range of MMTS tablet sizes
  - Flexible dose delivery (capsules, sachet, sprinkles)
- **Commercially proven**: successfully developed Zenpep (Allergan)
  - treatment of pancreatic enzyme insufficiency due to cystic fibrosis
Case Study: Gastrostomy tube (G-tube) Reliably and Effectively delivery of drugs

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ZENPEP® FDA-approved pancreatic enzyme product (PEP) for exocrine pancreatic insufficiency (EPI) due to cystic fibrosis (CF) and other conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEED</td>
<td>PEPs are administered through feeding tubes when oral administration is not feasible or convenient&lt;br&gt;Current clinical practice is based on clinical experience and anecdotal evidence and very few published data are available to support medication administration through G-tubes.&lt;br&gt;Pancreatic enzymes (i.e. Lipase, Protease and Amylase) are very sensitive and they could be inactivated if exposed to gastric environment</td>
</tr>
<tr>
<td>SOLUTION</td>
<td>PEP in the form of Eurand Minitabs® and Microtabs&lt;br&gt;Suitable for being administered through G-Tube without clogging and being damaged&lt;br&gt;Uniform gastro-protective coating non impacted by contact with nutritional fluid and the clinical practice</td>
</tr>
</tbody>
</table>
Purpose of the study

- Identification of a reliable and easy to handle method of administering Pancreatic Enzyme Replacement Therapy using G-tubes
- Investigation of delivery of Zenpep and Ultresa, obtained with MMTS™ technology
- Different typology of nutritional fluids, syringes and G-tubes were investigated
## Use of Pancreatic Enzyme Supplements

### Zenpep Microtablets
- **Type of beads:** Microtablets
- **Syringe tip/volume:** Catheter tip/35 ml
- **G-tube type:** Mic Bolus
- **External diameter:** 18 Fr

### Ultresa Minitablets
- **Type of beads:** Minitablets
- **Syringe tip/volume:** Slip tip/20 ml
- **G-tube type:** Mic Bolus
- **External diameter:** 20 Fr

### Creon Pellets (extruded beads)
- **Syringe tip/volume:** Slip tip/20 ml
- **G-tube type:** Mic Bolus
- **External diameter:** 18 Fr

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Coating Integrity

- Visual inspection of the G-tubes after pancreatic enzymes administration demonstrated that **G-tube patency was unaffected** and beads were deliverable without sticking and tube clogging.

- **Enteric coating of the beads remained intact** after the passage through G-tube since no appreciable difference between untreated and administered beads was found in terms of dissolution performances.
Future Trends: Ultra Microtablets

- As a result of the smaller size, **Ultra Microtablets** placebo (1.2 mm and 1.0 mm) are **deliverable by slip tip syringes**
- Mic-Key G-Tubes with **16Fr diameter revealed suitable** to allow the passage of both size of beads (1.2 mm and 1.0 mm)

<table>
<thead>
<tr>
<th>Product (size of beads)</th>
<th>Syringe tip/volume (ml)</th>
<th>G-tube type</th>
<th>External diameter (Fr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra Microtablets (1.2 mm)</td>
<td>Slip tip/10 and 20 ml</td>
<td>Mic-Key</td>
<td>16</td>
</tr>
<tr>
<td>Ultra Microtablets (1.0 mm)</td>
<td>Slip tip/10 and 20 ml</td>
<td>Mic-Key</td>
<td>16</td>
</tr>
</tbody>
</table>

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DIFFUCAPS® Customized Release Technology - Timed Pulsatile Release

CASE STUDY
Innopran XL® - Chronotherapy Release
Diffucaps® - Optimize Therapeutic Performance

- Drug core layered with one or more rate-controlling polymer blends
- Multiparticulate system
  - Sophisticated control of drug delivery
  - Single drugs and drug combinations

**Timed Pulsatile Release**
- Timed Polymer
- Seal-Coat Polymer
- Release
  - Pulse
  - Delay

**Timed Sustained Release**
- Timed Polymer
- Sustained-Release Polymer
- Release
  - Sustained
  - Delay

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Multiparticulate System and Timed Pulsatile Release

Formulation Flexibility to Target a Tailored PK profiling

Longer lag with slow release rate

Shorter lag time

Sharper pulse with longer lag
Case Study: Innopran XL®
How to ensure drug release when needed most

<table>
<thead>
<tr>
<th>DRUG</th>
<th>• Propanolol hydrochloride is a beta-blocker indicated for the treatment of hypertension, to lower blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEED</td>
<td>• Develop a once-daily, modified release dosage form releasing in the early morning hours when the patient is usually at greatest risk of high systolic blood pressure</td>
</tr>
<tr>
<td>SOLUTION</td>
<td>• Innopran XL® <strong>customized release beads</strong> delivering drug at early morning hours</td>
</tr>
<tr>
<td></td>
<td>• Commercial presentation: hard gelatin capsules filled with <strong>Diffucaps® XL</strong> beads for 80 mg and 120 mg strengths</td>
</tr>
</tbody>
</table>

InnoPran XL® is a registered trademark of ANI Pharmaceuticals, Inc. Diffucaps® is a registered trademark of Adare Pharmaceuticals S.r.l.
Cardiovascular events - Circadian Clock Dependent


Chronotherapeutic Propanolol to synchronize drug administration/delivery with circadian rhythms in order to optimize efficacy and/or minimize side effects
The objective of chronotherapy for hypertension is to **deliver more drug during early morning post-awakening when blood pressure is high** and less drug during the middle of the sleep cycle when BP is low.

**Traditional sustained release** agents (e.g. Inderal® LA), which deliver a near-constant drug concentration, **do not meet the needs for chronotherapy in hypertension**

**InnoPran XL®** (Propranolol CRR) has been designed, based on extensive modeling, to **provide tailored chronotherapy** in hypertension to complement the circadian pattern, thus **reducing vulnerability to morning cardiovascular events**

InnoPran XL® is a registered trademark of ANI Pharmaceuticals, Inc. Inderal® LA is a registered trademark of ANI Pharmaceuticals, Inc.
Simulated steady state profiles after oral administration of 1 TPR cps every 24h
In vivo results: Chronotherapy with InnoPran XL®

Plasma Profiles of InnoPran XL® versus Inderal® LA

InnoPran XL® is a registered trademark of ANI Pharmaceuticals, Inc. Inderal® LA is a registered trademark of ANI Pharmaceuticals, Inc.
With a Broad Range of Oral Formulation Technologies…

….We Can Help Transform Your Products

- Overcome complex formulation challenges
- Differentiate commercialized products and products in development
  - Improve patient convenience
  - Address specific patient populations
  - Optimize release profiles for new therapeutic uses
- Add valuable IP
Meet us at Booth #14

To learn more, please contact:
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Luigi.Boltri@adarepharma.com