Developing treatment options for patients with rare gastrointestinal and endocrine disorders and unmet medical needs…

Roger Garceau
*Senior Vice President and Chief Medical Officer*

*Treating rare diseases…*
*Transforming lives…*
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September 2010
Why investing in the orphan drug marketplace makes sense...
Orphan and niche indications offer a number of favorable dynamics

- **Market exclusivity**
  - The Orphan Drug Act grants seven years of market exclusivity from date of approval

- **Favorable pricing and reimbursement potential**
  - High unmet need, relatively small patient prevalence, and fewer reimbursement hurdles

- **Lower clinical trial costs**
  - Smaller studies
  - Potential for ‘repurposing’ already-approved therapies

- **R&D costs of orphan drugs are typically much lower than that of standard drugs**
  - Potential for conditional approvals

- **Lower marketing costs**
  - Focus groups mainly include specialist physicians and patient advocacy groups

- **Priority review and/or fast track potential**
Healthcare reform may benefit orphan drug developers...

- Orphan drugs are *exempt* from the annual fees imposed on manufacturers of branded prescription drugs for federally funded programs

- Orphan drugs are *exempt* from most required discounts for new entities covered by the 340B Drug Discount Program

...but discounts to fill the Medicare “donut hole” may impact profits

- Companies will be required to offer discounts for branded drugs to fill in the “donut hole” for Medicare Part D enrollees

Source: L.E.K. Research
Payors are unlikely to significantly influence orphan pricing - despite pressure in other disease states

- Low impact of orphan drugs on overall reimbursement spending
  "... Payers see [fewer] orphan candidates because if there are only a few thousand candidates in the U.S. with a certain need, these patients are even further spread out amongst payors …"  
  Medical Director at Blue Cross Blue Shield, MS

- Limited contracting with orphan drugs due to low patient prevalence

- Payors will cover orphan drugs to avoid negative publicity from denying treatment for rare and often serious conditions
  "... You don’t want to be on the cover of the Boston Globe saying that your company won’t cover these rare diseases …"  
  Pharmacy Director at Harvard Pilgrim, MA

- Incentive to reimburse these drugs due to potential offset of high medical care costs they aim to prevent
  "... For orphans, these are sick patients, if you don’t treat them, they can run a hospital bill equivalent to drug costs …"  
  Pharmacy Director at Harvard Pilgrim, MA

Source: Patient Protection and Affordable Care Act, In Vivo, Mondaq Business Briefing, Medical Marketing & Media, Inside Health Reform, L.E.K. research

Orphan drugs will likely not be affected by pricing and reimbursement pressures in the near-term
NPS strategy for success…
After a regulatory setback for its lead product candidate, NPS executed an aggressive strategic transformation...

- Discontinued investment in early-stage discovery research
- Implemented an outsourcing-based business model
  - Increase efficiencies and reduce overhead costs
- Shifted the therapeutic focus from large primary care markets to rare gastrointestinal and endocrine disorders with high unmet medical needs
  - Few, if any, therapeutic options
  - Limited competition
  - Treatment by physician specialists with well-defined medical markets
  - NPS could successfully launch both compounds independently
- Focus on North American markets only
- Utilize partnerships to participate in the commercial success of therapeutic areas and geographies outside of core focus
Lead indication for GATTEX is the treatment of parenteral nutrition dependent short bowel syndrome

- Short bowel syndrome (SBS) results from surgical resection, congenital defect or disease-associated loss of absorption
  - Characterized by the inability to maintain protein-energy, fluid, electrolyte or micronutrient balances on a conventional diet
  - Patients require intravenous feeding or parenteral nutrition (PN)
- Orphan indication
  - ~10,000 to 15,000\(^1\) patients in the U.S.
- High unmet medical need
  - PN is current standard of palliative care

### Challenges of PN-dependence
- IV drip up to 7 nights/week; 8-12 hrs/night
- Co-morbidities: liver damage, line sepsis, central venous thrombosis
- Low quality-of-life
- Direct cost $100,000+ per patient per year

### Benefits of intestinal rehabilitation
- Reduction or elimination of PN dependence
- Improved nutrition and hydration
- Improved quality-of-life
- Reduction of direct and indirect costs

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\(^1\) AGA Technical Review on SBS & Intestinal Transplantation; Gastroenterology 2003;124:1111 – 1134 and NPS market research
Second Phase 3 registration study of GATTEX (STEPS) fully randomized; results on track for early 2011

STEPS Registration Study

- GATTEX 0.05 mg/kg/day (n=43)
- Optimization & stabilization
- 1-4 months

STEPS 2 Extension Study

- GATTEX 0.05 mg/kg/day
- 6 months

- Placebo (n=43)
- 1-4 months

- GATTEX 0.05 mg/kg/day
- 24 months

- Primary endpoint: 20% reduction of PN at week 20 from baseline and maintained at week 24
- 35+ sites in US, EU, and Canada
- After STEPS, patients can enter STEPS 2 for 24 months of GATTEX
- Fully randomized (1:1) at 86 patients
- Patients still in optimization-stabilization phase bypass STEPS and will be enrolled in STEPS 2
- Estimated cost of STEPS: ~$25-30M
- Estimated cost of STEPS 2: ~$10-15M
- Nycomed sharing external costs and providing operational support
Short bowel syndrome is a rare disorder that could represent a significant commercial opportunity

<table>
<thead>
<tr>
<th>Rare &amp; chronic disorder</th>
<th>10 to 15 thousand PN-dependent SBS patients in the U.S.</th>
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<td>Orphan drug status with 7 years exclusivity</td>
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<tr>
<th>Significant unmet need</th>
<th>Parenteral nutrition (PN) is palliative</th>
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<td></td>
<td>Direct cost of PN exceeds $100K per year</td>
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<td>PN-related complications increase burden</td>
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<td>PN significantly hinders quality-of-life</td>
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<tr>
<th>Favorable market dynamics</th>
<th>Limited competition</th>
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<td>KOL-driven market</td>
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<td></td>
<td>Motivated patients desperately seeking solutions</td>
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<td>Positive reimbursement outlook; pricing inelasticity</td>
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<th>Unique mechanism of action</th>
<th>GI-specific mechanism of action</th>
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<td></td>
<td>Clinical benefits for SBS</td>
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<td>Potential to expand in additional intestinal rehabilitation related conditions</td>
</tr>
</tbody>
</table>
Teduglutide’s broad therapeutic spectrum could offer multiple opportunities in orphan indications

Teduglutide, a novel mucosally active analog of glucagon-like peptide-2 (GLP-2) for the treatment of moderate to severe Crohn’s disease. Inflammatory Bowel Diseases, 2010; 16(6):962-73

<table>
<thead>
<tr>
<th>Indication</th>
<th>Status</th>
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<tbody>
<tr>
<td>Chemotherapy-induced GI mucositis</td>
<td>▪ Pre-IND meeting held with FDA</td>
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<tr>
<td></td>
<td>▪ Defining a clinical development strategy</td>
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<tr>
<td>Pediatric SBS</td>
<td>▪ Preclinical studies substantially complete</td>
</tr>
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<td></td>
<td>▪ Potential synergies with Nycomed’s pediatric investigation plan</td>
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<td>Malabsorption disorders</td>
<td></td>
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<tr>
<td>Febrile neutropenia</td>
<td></td>
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<tr>
<td>Radiation-induced GI mucositis</td>
<td></td>
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<tr>
<td>Ulcerative colitis</td>
<td></td>
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<tr>
<td>Additional pediatric indications:</td>
<td></td>
</tr>
<tr>
<td>▪ Necrotizing enterocolitis, acceleration of intestinal maturation, and congenital villous</td>
<td>▪ Under evaluation</td>
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Intestinal failure is characterized by the inability to maintain protein, energy, fluid, electrolyte or micronutrient balance.
NPS is preparing to file a US marketing application for its lead product candidate in 2011.

- Two Phase 3 registration programs for specialty orphan indications
  - **GATTEX®** (teduglutide) for short bowel syndrome (SBS)
  - **NPSP558** (parathyroid hormone 1-84) for hypoparathyroidism

- Flexible outsourcing business model optimizes resources and limits financial exposure

- Internal programs complemented by valuable royalty-based portfolio for areas outside of core focus

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**Partially monetized** | **Unencumbered**
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Looking ahead at the rare disease market...
Orphan and niche indications are attractive, but the regulatory path is challenging

Annual U.S. orphan drug approvals and designations
1991-2009
Number of drugs

Note: * 2010 estimated based on approvals and designations up through 2009
Source: FDA, BCC Research, Business Insights, L.E.K. analysis
Changing regulatory requirements makes approval decisions on orphan drugs unpredictable

- Fewer positive recommendations for NCEs in 2010
  - More products are being reviewed by advisory committees given new requirements under FDAAA 2007**
  - Conflict of interest rules limit the available pool of experienced panel members for AC participation
- If this trend holds, orphan drug developers may face an increasingly challenging approval landscape
  - Given the rarity and complexity of some niche diseases, there may be a scarcity of experts

Notes: * As of August 2010; ** Food and Drug Administration Amendments Act of 2007
Source: Concept Capital, thestreet.com, L.E.K. analysis
Leveraging existing treatments for common diseases into rare diseases may offer favorable advantages

- FDA database launched in June 2010 aims to encourage orphan drug development through database of FDA-approved compounds and products that also show promise in rare diseases
  - Advantages to ‘repurposing’ already-approved products
- Orphan-designated products with at least one marketing approval for a common disease indication: ~180*
- Orphan-designated products with at least one marketing approval for a rare disease indication: ~170*
- Orphan-designated products with marketing approvals for both common and rare disease indication: ~100*

Large Unmet Need for New Treatments:
Despite the incentives in the Orphan Drug Act, there are only about 350 such drugs that have been approved — and there are some 7,000 rare diseases.**

* U.S. Food and Drug Administration Rare Disease Repurposing Database (RDRD) data
Orphan Drug designation can be leveraged to extend runway on blockbusters

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Drug</th>
<th>Approved Common-Disease Indications**</th>
<th>Approved Orphan-Designated Indications**</th>
<th>Orphan Designated Indications Pending Approval**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALLERGAN</strong></td>
<td>Botox®</td>
<td>Temporary improvement in the appearance of moderate to severe frown lines in adult patients ≤ 65 years of age.</td>
<td>Eyelid twitching associated with dystonia in adults (patients ≥12)</td>
<td>Dynamic muscle contracture in pediatric cerebral palsy patients</td>
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<td></td>
<td></td>
<td>Upper limb spasticity in adult patients.</td>
<td>Cross-eyes or lazy eye associated with dystonia in adults (patients ≥12)</td>
<td>Synkinetic closure of the eyelid associated with VII cranial nerve aberrant regeneration</td>
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<tr>
<td></td>
<td></td>
<td>Severe underarm sweating in adult patients.</td>
<td>Cervical dystonia in adults</td>
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<td><strong>Abbott</strong></td>
<td>Humira® adalimumab</td>
<td>Rheumatoid Arthritis</td>
<td>Moderately to severely active polyarticular juvenile idiopathic arthritis (patients ≥4 yrs)</td>
<td>Pediatric Crohn's disease</td>
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<td></td>
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<td>Psoriatic Arthritis</td>
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<td>Ankylosing Spondylitis</td>
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<td>Crohn’s Disease</td>
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<td>Plaque Psoriasis</td>
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<td><strong>Bristol-Myers Squibb</strong></td>
<td>Erbitux® cetuximab</td>
<td>Refractory EGFR-expressing metastatic colorectal cancer</td>
<td>Squamous cell carcinoma of the head and neck in combo with radiation therapy</td>
<td>Pancreatic cancer</td>
</tr>
<tr>
<td><strong>ImClone Systems Incorporated</strong></td>
<td></td>
<td></td>
<td>Recurrent or metastatic squamous cell carcinoma of the head and neck</td>
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* U.S. Food and Drug Administration Rare Disease Repurposing Database (RDRD) data  
** Full label information truncated for length
Future of orphan drug development will continue to evolve the space

Increased focus from big Pharma will heighten interest

Abbott webcast states commitment to rare diseases
Novartis discusses commitment to rare diseases as part of Rare Disease Day
Pfizer establishes a research group focused on rare diseases
Pfizer announces acquisition of FoldRx for rare disease unit

Bayer Healthcare’s sustainable healthcare report describes research efforts into rare diseases
GSK announces new standalone unit specializing in the development and commercialization of medicines for rare diseases
Sanofi-Aventis sought to acquire Genzyme in an effort to move into rare diseases

Currently marketed orphan drugs in the U.S. by select Big Pharma*

<table>
<thead>
<tr>
<th>Company</th>
<th>Number of Drugs</th>
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<tr>
<td>Eli Lilly</td>
<td>4</td>
</tr>
<tr>
<td>GSK</td>
<td>9</td>
</tr>
<tr>
<td>J&amp;J</td>
<td>2</td>
</tr>
<tr>
<td>Merck</td>
<td>1</td>
</tr>
<tr>
<td>Novartis</td>
<td>9</td>
</tr>
<tr>
<td>Pfizer</td>
<td>5</td>
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* Non-comprehensive list
Source: NPS Strategic Research
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Thank you and questions
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nps
pharmaceuticals

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Transforming lives...