PolyXen™: A Polysialylation Technology for Enhancing Therapeutic Proteins and Its Clinical Application

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Overview

• Clinical-stage biopharmaceutical company focused on discovery, research and development of next-generation biologic drugs and novel orphan oncology therapeutics

• PolyXen™ - proprietary polysialic acid (PSA) drug delivery platform expected to drive near term licensing revenue
  - Enables next generation biologic drugs by improving their half-life and other pharmacological properties

• XBIO-101 (sodium cridanimod) - lead program in Phase 2 clinical development for treatment of progesterone resistant endometrial cancer (EC)

• Out-licensing agreement with Shire for SHP656 (PSA- recombinant Factor VIII) for treatment of hemophilia A

• Robust IP portfolio with over 200 patents issued or allowed
Business Model

Therapeutic Development
- Internal clinical development programs focused on repurposed drugs for oncology indications
- Develop programs through key inflection points
- Regional licensing agreements designed to de-risk development programs

Platform Technology
- PolyXen: Proprietary enabling platform technology for next-generation protein drug delivery
- Out-license opportunities to generate non-dilutive capital
- PolyXen Partnerships
  - Shire: Factor VIII (hemophilia)
  - SIIL*: EPO

*Serum Institute of India
PolyXen PSA Technology Platform

- Advantages of PolyXen Technology
- cGMP Manufacturing
- Physiochemical and Biological Properties of PSA & Polysialylated Proteins
- Clinical Use Cases
PolyXen: Enhancing Protein Drugs

- Polysialylation employs the natural polymer polysialic acid (PSA) to modulate the pharmacokinetic and pharmacodynamic properties of protein drugs
- Modelled on the multi-billion dollar success of PEGylation, which uses the synthetic polymer polyethylene glycol (PEG)

**Key Features:**
- Half-life extension
- Retention of native protein conformation
- Non-immunogenicity
- Biodegradability
- Low viscosity
- Fewer injections
- Improved protease stability
- Improved thermal stability
- Broad patent coverage

**Versatile:**
- Designed to improve the clinical utility of most protein and peptide drugs
- Applicable to franchise extensions as well as candidates in development
- Potential use for delivering small molecule drugs
Polysialylation is an alternative to PEGylation and other platforms

<table>
<thead>
<tr>
<th>Commercial name</th>
<th>Drug name</th>
<th>Company</th>
<th>PEG size (Da)</th>
<th>Indication</th>
<th>Year of approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adagen®</td>
<td>Pegadamsnase</td>
<td>Enzon</td>
<td>Multiple linear 5000</td>
<td>SCID</td>
<td>1990</td>
</tr>
<tr>
<td>Oncaspar®</td>
<td>Pegaspargnase</td>
<td>Enzon</td>
<td>Multiple linear 5000</td>
<td>Leukemia (ALL, CML)</td>
<td>1994</td>
</tr>
<tr>
<td>PEG-INTRON®</td>
<td>Peginterferon-α2b</td>
<td>Schering-Plough</td>
<td>Linear 12,000</td>
<td>Hepatitis C</td>
<td>2000</td>
</tr>
<tr>
<td>PEGASYS®</td>
<td>Peginterferon-α2a</td>
<td>Hoffman-La Roche</td>
<td>Branched 40,000</td>
<td>Hepatitis C</td>
<td>2001</td>
</tr>
<tr>
<td>Neulasta®</td>
<td>Pegfiligrastim</td>
<td>Amgen</td>
<td>Linear 20,000</td>
<td>Neutropenia</td>
<td>2002</td>
</tr>
<tr>
<td>Somavert®</td>
<td>Pegvisomant</td>
<td>Pharmacia &amp; Upjohn</td>
<td>4–6 linear 5000</td>
<td>Acromegaly</td>
<td>2003</td>
</tr>
<tr>
<td>Macugen®</td>
<td>Pegaptanib</td>
<td>Pfizer</td>
<td>Branched 40,000</td>
<td>Age-related macular degeneration</td>
<td>2004</td>
</tr>
<tr>
<td>Mircera®</td>
<td>mPEG-eopetin-β</td>
<td>Hoffman-La Roche</td>
<td>Linear 30,000</td>
<td>Anemia associated with chronic renal failure</td>
<td>2007</td>
</tr>
<tr>
<td>Cimzia®</td>
<td>Certolizumab pegol</td>
<td>UCB</td>
<td>Branched 40,000</td>
<td>Reducing signs and symptoms of Crohn’s disease</td>
<td>2008</td>
</tr>
<tr>
<td>Puricase®/Krystexxa®</td>
<td>PEG-uricase</td>
<td>Savient</td>
<td>10,000</td>
<td>Gout</td>
<td>2010</td>
</tr>
<tr>
<td>Movantik</td>
<td>Naloxegol</td>
<td>AstraZeneca</td>
<td>339</td>
<td>Opioid-induced constipation</td>
<td>2014</td>
</tr>
</tbody>
</table>
Potential Limitations of PEG: Toxicity

- PEG is non-biodegradable
  - Some evidence of a low rate of enzyme-mediated oxidation
  - Aldehydes and ketones generated in the body, not eliminated by normal detoxification mechanism

- PEGylation of therapeutic proteins could lead to:
  - Accumulation in tissues – vacuolization
  - Likely problematic for protein therapeutics administered in large amounts and/or chronically

- Rheological Properties of PEG

Bendele et al., Renal tubular vacuolation in animals treated with PEG conjugated proteins, Toxicological sciences, 42 (1998) 152-157
Potential Limitations of PEG: Immunogenicity

Clinical and Regulatory Considerations

• 25-30% of patients have pre-existing anti-PEG neutralizing antibodies

• Induction of anti-PEG antibodies against PEGylated proteins (reported clinical cases)
  - PEG-asparaginase and PEG-uricase

• FDA guidelines recommend screening for anti-PEG antibodies when evaluating the potential immunogenicity of PEGylated proteins (2014)

• EMA recommends that care be used in PEGylated products for the pediatric population (2012)

PolyXen Exploits Nature

- PolyXen employs the linear $\alpha 2-8$ polymer of sialic acids (colominic acid)
- Hydrophilic polymer from *E. coli* strain K1
- Natural glycan
- Negatively charged
- Highly evolved immune evasion properties
- Limited toxicity
- Sialic acid to 100KDa PSA

PolyXen: Patents & Patent Applications

Granted patents & patent applications covering PSA including:
Use, Manufacturing, Chemistry, and New Molecular Entities

• Use of PSA for drug delivery
  - Polysaccharide B in DDS (base patent)
  - Monofunctional PSA
  - Polysialylation in SDS

• Manufacturing
  - Manufacturing of PSA
  - Fractionation of PSA
  - Endotoxin Removal

• Modalities of attachment
  - NHS functional PSA
  - NHS amino PSA fractions
  - Thiol-reactive PSAs
  - N-terminal polysialylation

• Selected PSA constructs
  - Polysialylated EPO
  - Polysialylated insulin
  - Polysialylation of non-blood coagulation factors
  - Polymer protein conjugates
PolyXen: Commercial cGMP Manufacturing
Serum Institute of India

- India’s leading biotechnology company
- World’s largest vaccine manufacturer by number of doses produced
- cGMP manufacturing facility accredited by World Health Organization
- Manufactures cGMP grade PSA for Xenetic and its partners
Manufacturing of PSA-Protein Conjugates

- PSA chains can vary in length
- Conjugation can be site-directed or random
Controlled Fractionation of PSA by Acid Hydrolysis & AEX
## Release Specifications of Oxidized PSA

<table>
<thead>
<tr>
<th>No.</th>
<th>Parameter</th>
<th>Method of Analysis</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Appearance</td>
<td>Visual inspection</td>
<td>White or ivory white powder, freely soluble and free from particulate matter when dissolved in water</td>
</tr>
<tr>
<td>2</td>
<td>Loss on drying</td>
<td>Thermogravimetric</td>
<td>Not more than 5%</td>
</tr>
<tr>
<td>3</td>
<td>Absolute molecular weight</td>
<td>Gel permeation chromatography (GPC) using Viscotek</td>
<td>MW ± 15%</td>
</tr>
<tr>
<td>4</td>
<td>Polydispersity index</td>
<td></td>
<td>1.00-1.10</td>
</tr>
<tr>
<td>5</td>
<td>Purity</td>
<td>GPC</td>
<td>Not less than 95%</td>
</tr>
<tr>
<td>6</td>
<td>Chemical functionality</td>
<td>Glucose assay</td>
<td>80-120%</td>
</tr>
<tr>
<td>7</td>
<td>pH</td>
<td>pH meter</td>
<td>6–8 in WFI with a conc. of 1 mg/mL</td>
</tr>
<tr>
<td>8</td>
<td>Structural identity</td>
<td>NMR</td>
<td>Spectrum identical to that of alpha 2,8-linked polysialic acid</td>
</tr>
<tr>
<td>9</td>
<td>Phosphate content</td>
<td>AMES method</td>
<td>Not more than 1.3 mole PO₄/mole PSA</td>
</tr>
<tr>
<td>10</td>
<td>Heavy metals</td>
<td>European pharmacopeia method</td>
<td>Report value in ppm</td>
</tr>
<tr>
<td>11</td>
<td>Endotoxin content</td>
<td>Limulus amoebocyte lysate method (KTA)</td>
<td>Not more than 4 EU/100 mg of PSA</td>
</tr>
<tr>
<td>12</td>
<td>Bioburden</td>
<td>Pharmacopeia method</td>
<td>Not more than 10 CFU/g of PSA</td>
</tr>
</tbody>
</table>

(Additional testing on GMP grade oxidized PSA for residual or process extractable impurities, O-acetylation, free amino groups, sodium content, Ca content and ethanol content may be performed if required)
PSA: Physiochemical and Biological Properties
Polysialic Acid is Biodegradable

**Hydrolysis of PSA in liver homogenate**

**Polysialic Acid**

- *In vivo* lysosomal degradation
- Acid hydrolysis (pH 5.5, 37°C)
- Neuraminidase

**Sialic Acid**

** PSA (MW 21.4 KDa)**

- Signal intensity
- Retention time (minutes)
- AEX

- 0 h, 4 h, 16 h, 62 h
Polysialylation Confers Protection Against Serum Proteases

Incubation in Fetal Bovine Serum

- Asparaginase
- Polysialylated asparaginase

Relative enzyme activity (%) vs. Time (h)
Polysialylation is effective in maintaining the PK profile of asparaginase in the presence of anti-drug antibodies (in vivo)

<table>
<thead>
<tr>
<th>Proteins</th>
<th>Naïve Mice</th>
<th>Pre-Immunized Mice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$t_{1/2}, \beta$ (h)</td>
<td>Log IgG titers</td>
</tr>
<tr>
<td>Asparaginase</td>
<td>15.27 ± 1.45</td>
<td>n.a.</td>
</tr>
<tr>
<td>PSA-Asparaginase</td>
<td>37.76 ± 1.39</td>
<td>n.a.</td>
</tr>
</tbody>
</table>
PSA Reduces Antibody Recognition

PSA-Insulin retains biological activity in presence of anti-Insulin antibodies

(in vivo)

Regulation of glucose by insulin and PSA-insulin in mice

Regulation of glucose by insulin and PSA-insulin in mice after pre-incubation with anti-insulin antibodies
PSA-DNase: Enhanced Thermal Stability

Dynamic Light Scattering:
- Polysialylation results in increased thermal stability of DNase
Circular Dichroism:
- Conformation of PSA-EPO is similar to EPO
- PSA-EPO has higher thermal stability than EPO
ErepoXen™ (PSA-EPO) Clinical Trial
ErepoXen (PSA-EPO)

• Xenetic’s most advanced in-house PSA-protein program

• Ongoing Phase 2/3 clinical trials:
  - India, Russia, Australia, New Zealand, South Africa

• Readouts include safety, tolerability, immunogenicity, efficacy

• Single dose (s.c.) Phase 1/2 completed in India (~120 subjects)

• Repeat dosing (s.c.) Phase 2 in progress in Australia & South Africa (~40 subjects to date)
PK of PSA-EPO in CKD Subjects (Phase 2)

Dose Response & PK Data (source: SIIL)

Days of Treatment

PSA-EPO (ng/ml)

- SII 0.5 ug/kg
- SII 1.0 ug/kg
- SII 2.0 ug/kg
## Half-Life Extension of EPO by Polysialylation

### Half-life of various erythropoiesis stimulating agents in man

<table>
<thead>
<tr>
<th>Company: Drug</th>
<th>Population</th>
<th>Route</th>
<th>Half-Life (avg. hrs.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AMGEN: Epogen®</strong></td>
<td>Healthy Subjects</td>
<td>s.c.</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>PD patients</td>
<td>s.c.</td>
<td>4-13</td>
</tr>
<tr>
<td><strong>AMGEN: Aranesp®</strong></td>
<td>-</td>
<td>s.c.</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>PD patients</td>
<td>s.c.</td>
<td>49</td>
</tr>
<tr>
<td><strong>ROCHE: Mircera®</strong></td>
<td>Healthy Subjects</td>
<td>s.c.</td>
<td>137</td>
</tr>
<tr>
<td></td>
<td>PD patients</td>
<td>s.c.</td>
<td>140</td>
</tr>
<tr>
<td><strong>XENETIC: ErepoXen®</strong></td>
<td>Healthy Subjects</td>
<td>s.c.</td>
<td>121</td>
</tr>
<tr>
<td></td>
<td>PD patients</td>
<td>s.c.</td>
<td>&gt;400</td>
</tr>
</tbody>
</table>

Data for marketed ESAs referenced from company prescribing information brochure or EMA disclosure documents.
Clinical Results from ErepoXen Trials

ErepoXen Dosing:
Once every two weeks during the correction phase
Once every four weeks during maintenance

• ErepoXen is effective at increasing and maintaining Hb to therapeutic level
• No significant side effects have been observed from clinical trials
• No toxicity found in formal toxicity studies of PSA-EPO
• No PSA or PSA-EPO immunogenicity observed to date
PolyXen PSA Technology Platform: Summary

- Enables next-generation protein & peptide therapeutics
- GMP manufacturing methods established
- Clinically demonstrated to Phase 2
- Xenetic is pursuing internal programs and out-license opportunities related to:
  - New Molecular Entities
  - Lifecycle management
Thank you

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