The Next Generation in Polymer Therapeutics

Randall W. Moreadith, MD, PhD
President and CEO

Neurotech Investing and Partnering Conference
May 1-2, 2018
Boston, MA
“A completely synthetic polymer that has virtually unlimited capacity for drug load, can be programmed for targeting, is non-immunogenic, does not accumulate in the body and can prolong the half-life of proteins as well as small molecules. This will be bigger than PEGylation”

- Mike Bentley, Co-Founder, Serina
Serina Management

J. Milton Harris, PhD and Michael Bentley, PhD
Co-Founder, Chairman Co-Founder, CSO

- Milton Harris founded Shearwater Polymers in 1992; Mike joined in 1997
- Sold to Inhale Therapeutics in 2001 for $200M (Nektar Therapeutics)
- Co-inventor on multiple PEG patents – Ushered in the 1st generation PEG technology
- 13 approved products = Over $150B (Neulasta, Pegasys, Macugen, Movantik, Plegridy, Cimzia, Somavert)

Randall Moreadith, MD, PhD
President and CEO

- Former Chief Development Officer, Nektar Therapeutics
- Co-Founder, Thrombogenics, Ltd.
- 22 Year Biotechnology Executive
- Led $30M raise at Serina – All from local shareholders in Huntsville, AL

Tacey Viegas, PhD and Brendan P. Rae, JD, PhD
Chief Operating Officer Chief Business Officer

- Senior executives in the pharma industry for > 20 years
- Experts in CMC, drug delivery, partnering and licensing
POZ vs PEG - Next generation technology avoids limitations in PEG

**POZ**
- Safe, inexpensive starting materials
- Does not form peroxides
- POZ – “one pot synthesis”
- Stable at RT, refrigerator, -20 C
- Relatively low viscosity
- High, programmable drug loading
- Active targeting of pendent POZ
- Excreted unchanged (renal)
- Non-immunogenic
  - Absence of pre-formed antibodies to POZ is anticipated
- Minimal tissue accumulation
  - Only observed in monkey at 20X HED
- Patent estate (largely to Serina)

**PEG**
- Explosive, toxic starting materials
- Forms peroxides (must add BHT)
- Limited suppliers of quality PEG
- Stable only at < -20 C
- Relatively high viscosity
- Low drug loading
- Difficult to actively target
- Major route of elimination renal
- Pre-formed Abs in ~25% population
  - Antibodies to PEG are suspected to alter response to some products
- Tissue accumulation (multiple)
- Immunogenicity of mPEG products
- Crowded patent estate
How we make POZ for small molecules

- Programmable loading of polymer is determined by the ratio of pentynyl : neutral monomers at initial synthesis (example above is a 20 kDa 10 pendent POZ)

- IEC for purification takes advantage of the –COOH on the terminus of the polymer (Typically > 70% yields, PDI < 1.02, currently at 5 kg cGMP scale and scaling up for proprietary and partnered programs)
How we design POZ-therapeutics of small molecules

- **Thousands** of small molecules with the appropriate chemical handle (-OH group)
- Programmable loading of polymer during initial synthesis – Controlled drug loading at the “click chemistry” step
  - Single-step Cu(I)-catalyzed “click chemistry” at pendent alkyne
  - Serina holds the Global Exclusive License from the Scripps Research Institute for development of POZ-therapeutics
- Drug release is tuned by the nature of the ester linker attached to the drug (butyrylcholinesterase is the only esterase activity in human plasma that catalyzes release)
Chemical Structures of Pipeline Compounds
All have an accessible chemical handle

• Candidate small molecules must have a “chemical handle”
• Linkers are attached to the –OH, with an azide moiety at the other end for “click chemistry” attachment to the pendent alkyne
• In a database search of known chemical structures (AdisInsight) there are thousands of candidate molecules
The Pipeline

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SERINA THERAPEUTICS, INC.

SER-214 Target Product Profile
Comparison to short-acting oral formulations

- Short-acting oral dopaminergic agents have a limited therapeutic window
- Phasic “peak-trough” is problematic – “wearing off” and promotes dyskinesia
- A single weekly sc injection that would provide continuous drug delivery within the therapeutic window would represent a significant clinical advance
A Weekly SC Injection of SER-214
Provides Continuous Drug Delivery in Monkeys

- Cynomolgous macaque monkeys (~3 kg) received a single weekly SC injection of ~58 mg SER-214 (~7 mg equivalents rotigotine) / kg in a final volume of ~0.5 cc
- In weeks 1/5/9/12 daily plasma rotigotine levels were determined
- Following a slow rise to $T_{\text{max}}$ on Day 3-4 plasma levels of released rotigotine remained within a narrow range of 6-8 ng/ml without accumulation or accelerated clearance
## Phase Ia Study in Stably-treated Parkinson’s Patients

Asses safety, tolerability and pharmacokinetics

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose of SER-214 (SC)</th>
<th>Data Collected</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Single 20 mg</td>
<td>Safety, PK</td>
</tr>
<tr>
<td>1</td>
<td>50 mg (beginning of each week for 2 consecutive weeks)</td>
<td>Safety, PK</td>
</tr>
</tbody>
</table>
| 2      | 50 mg (beginning of Week 1)  
100 mg (beginning of Weeks 2 and 3) | Safety, PK     |
| 3      | 50 mg (beginning of Week 1)  
100 mg (beginning of Week 2)  
200 mg (beginning of Weeks 3 and 4) | Safety, PK     |

- Establish **safety and tolerability** of a weekly injection of SER-214 in Parkinson’s Disease patients
  - Safety endpoints will establish if a weekly injection of SER-214 would be safe in PD patients who are either naïve to PD drugs, or on a stable regimen of PD medications
- Establish if a weekly sc injection of SER-214 provides predictable levels of rotigotine within the therapeutic window for relief of symptoms
- Establish **efficacy** of SER-214 in providing symptomatic relief of mild motor fluctuations
  - Unified Parkinson’s Disease Rating Scale (UPDRS)
  - Motor portions of UPDRS (Parts II and III) constitute the approvable endpoint for all new PD drugs in development
A Weekly SC Injection of SER-214 Provides Continuous Drug Delivery in Humans

- Data from Cohort 3 in the multiple dose portion of the Phase Ia trial in Parkinson’s disease
- Patients received: an initial subcutaneous dose of 50 mg SER-214; 100 mg dose in Week 2; and 200 mg in Week 3 and Week 4
- Plasma levels of released rotigotine are shown for Week 3 and Week 4 and compared to the 3 mg Neupro patch – the highest approved dose for RLS in the US
A Weekly SC Injection of SER-214
Dose-dependent Increase in Continuous Drug Delivery in Humans

Effect of dose on steady-state (Css) levels of rotigotine in Parkinson's patients following weekly sc of SER-214 (mean, ±SD; n=5)

<table>
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<tr>
<th>Dose of SER-214 (mg)</th>
<th>Css (ng/mL)</th>
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<tr>
<td>0</td>
<td>0.0</td>
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<tr>
<td>100</td>
<td>0.2</td>
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<td>200</td>
<td>0.4</td>
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<tr>
<td>300</td>
<td>0.6</td>
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<tr>
<td>400</td>
<td>0.8</td>
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\[ y = 0.00208 - 0.028 \]
\[ r^2 = 0.999 \]

extrapolated

- Data from Cohorts 1, 2 and 3 in the multiple dose portion of the Phase Ia trial in Parkinson’s disease
- Mean +/- SD of steady-state release of rotigotine in the two week period for repeat doses
- Extrapolation to a 2-3 mL injection of SER-214 would provide steady-state that would approximate the 8 mg Neupro patch – the highest approved dose for PD in the US
A Weekly SC Injection of SER-214
Dose-dependent Decline in UPDRS (Part III)

Effect of dose on UPDRS part III scores in Parkinson’s patients following weekly sc of SER-214
(mean for n=5)

- Data from Cohorts 1, 2 and 3 in the multiple dose portion of the Phase Ia trial in Parkinson’s disease
- Change from baseline in UPDRS (Part III) as a function of dose
- The predicted change in UPDRS (Part III) at the 400 mg doses of SER-214 would hit the approvable endpoint for use of SER-214 for the PD indication
Apomorphine has many of the characteristics ideal for POZ

- **Apomorphine**
  - Accessible chemical handle(s)
  - Very limited solubility
  - Low bioavailability makes it unsuitable as an oral drug
  - Short half-life of < 5 minutes makes it unsuitable for IV administration
  - Present formulations limited by significant skin irritation through transcutaneous approaches
  - Attachment to POZ would keep the molecule on the polymer until it reached the blood – whereupon it would be cleaved immediately by BChE, thus providing steady-state release kinetics
**SER-214 Summary**

A single weekly subcutaneous injection of SER-214 is a significant advance for Parkinson’s disease and RLS patients

- In restless legs syndrome (RLS – 0.25 mL, 0.5 mL, 1.0 mL insulin syringe)
  - Improved compliance, markedly improved tolerability without skin reactions, less chance of augmentation, QoL issues, preliminary market research suggests it may assume second-line therapy after failure of oral dopamine agonists
- In Parkinson’s disease (PD – wearable device to deliver weekly injection over 5 minutes)
  - In early PD use of a device should yield levels of released rotigotine that would improve UPDRS (Part II and III)
  - In advanced PD SER-214 is predicted to reduce “off” time
  - Treat or prevent dyskinesia in patients with early motor complications

**Development pathway**

- 505(b)(2) – rely on the established safety/efficacy of Neupro
- Potential for a single PK comparability trial (Both RLS and PD indication)
- Commercial launch in 2023 for RLS and 2024 for PD
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Long acting analgesics - The future of post-operative pain management

The opioid epidemic has reached devastating levels in the USA

- Now the leading cause of accidental death in the USA - 115 people a day die of an overdose
- In 2012 - 300 million prescriptions for opioids were written in the USA – enough for every medicine cabinet in the US to have a bottle of prescription opioids
- In 2015 there were 75,000,000 prescriptions written for post-operative pain control from major surgical procedures
- 15% of patients who are prescribed an opioid for post-operative pain will transition to chronic use
- 31% of prescriptions for opioids are written by dentists – where opioids are often inferior in pain relief to NSAIDs
- The fastest rise in accidental death from opioids if occurring in the age group 12-17 … where they often get them from an unused bottle in the medicine cabinet

A long-acting candidate drug that would target the opioid epidemic in its tracks?
SER-226/227
Injectable for post-operative pain management

Buprenorphine

• Safety and efficacy profile is well established but not a commercial success for post-operative pain due to short half-life (6-12 hrs)
• 3 unique mechanisms of action
  • 30-50 X more potent than morphine
  • Functions as a Na-channel blocker
  • Inhibition of hyperalgesia at nociceptors in CNS and wound bed
• Buprenorphine blocks other opioids from binding to the MOR, marked prevention of euphoria
• TPP - POZ-buprenorphine would provide > 3 days of analgesia without the need to transition to oral opiates – and would prevent response to an opioid if you took it
Brennan Model in the rat
Gold standard post-operative pain model

Animals are allowed to recover from surgery. Test article is injected and a battery of tests are then applied to the wound area to assess withdrawal thresholds.
SER-226/227 - Immediate analgesia and prolonged duration

Mechanical allodynia threshold, incised hind paw

- Maximal effect of morphine and bupivacaine in Brennan model
  - At 2 hrs equivalent to morphine; at 5 hrs exceeds bupivacaine (Exparel)
  - Prolonged duration – gradually diminishes over 72 hrs
  - Exceeds activity of any known analgesic in this model
SER-227 – Monkey, > 3 days of release of buprenorphine

• Young adult male monkeys dosed SC with single injections of SER-226 or SER-227 at 1.5 mg/kg (SER-226 – 2-propionate linker, SER-227 – 3-propionate linker)
• PK levels were determined at 3, 6, 12 and 24 hrs – then daily for 10 days
• SER-227 provides steady-state levels of buprenorphine at the Rx level for > 3 days

PK Profile of Buprenorphine after SC dosing of SER-226 and SER-227 to male monkeys (Dose 1.5mg/kg; n=3; ±SD)

SER-227 entered IND-enabling toxicology in December Phase I Q3-2018
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Cannabis and Medical Applications

• Medical importance of extracts of Cannabis date back over 3,000 years
  • THC (tetrahydrocannabinol) is the psychotropic component (the “high”)
  • CBD (cannabidiol) is the second major component, non-psychotropic

• Both CBD and THC can be easily attached to POZ (single chemical handle – phenolic hydroxyl)

• Published study from Stanford University in 2013 suggested CBD could dramatically alter seizure frequency in childhood forms of epilepsy

• GW Pharma has submitted an NDA using oral cannabidiol formulation (Epidiolex®) to treat rare childhood forms of epilepsy (Lennox-Gastaut Syndrome and Dravet Syndrome) – PDUFA June 2018
  • Epidiolex is cannabidiol extracted from Cannabis plants suspended in sesame seed oil
  • Epidiolex is administered in divided doses twice / day
Cannabis and treatment-refractory epilepsy

- Refractory epilepsy in children and adults is a significant challenge
- As many as ~1M in the US and 20M worldwide are refractory
- Once you fail three AEDs, in general, there is not a significant response
  - Children in the 2013 Stanford study, in which parents were giving their children Cannabis derived oils, had failed from 6-15 AEDs
  - Medically refractory epilepsy in children often leads to severe mental handicap
- Treatment-refractory epilepsy is under-recognized and under-treated

New anti-epileptic medications are desperately needed
Immunotherapy

CBD treatment was associated with an increase in diarrhea, vomiting, fatigue and somnolence.

These side effects may be due to a $C_{\text{max}}$ effect of the dosage formulation.

Continuous drug delivery of CBD via a POZ-polymer will improve compliance, tolerability and efficacy.

Epidiolex
Treatment is associated with significant side effects

**Table 4. Adverse Events Occurring with a Frequency of Greater Than 10% in Either Trial Group, According to System Organ Class and Preferred Term.**

<table>
<thead>
<tr>
<th>System Organ Class and Preferred Term</th>
<th>Cannabidiol (N = 61)</th>
<th>Placebo (N = 59)</th>
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<tbody>
<tr>
<td>Gastrointestinal</td>
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<tr>
<td>Diarrhea</td>
<td>19 (31)</td>
<td>6 (10)</td>
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<td>Vomiting</td>
<td>9 (15)</td>
<td>3 (5)</td>
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<tr>
<td>General</td>
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<tr>
<td>Fatigue</td>
<td>12 (20)</td>
<td>2 (3)</td>
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<td>Pyrexia</td>
<td>9 (15)</td>
<td>5 (8)</td>
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<tr>
<td>Infections: upper respiratory tract</td>
<td>7 (11)</td>
<td>5 (8)</td>
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<tr>
<td>infection</td>
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<td></td>
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<td>Metabolism: decreased appetite</td>
<td>17 (28)</td>
<td>3 (5)</td>
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<td>Nervous system</td>
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<td>Convulsion</td>
<td>7 (11)</td>
<td>3 (5)</td>
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<td>Lethargy</td>
<td>8 (13)</td>
<td>3 (5)</td>
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<td>Somnolence</td>
<td>22 (36)</td>
<td>6 (10)</td>
</tr>
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*Events were classified according to the Medical Dictionary for Regulatory Activities, version 17.0.*
POZ-cannabidiol provides continuous drug delivery

- A single weekly SC injection of POZ-cannabidiol provides continuous drug delivery
- Bypasses first-pass metabolism
- Provides steady-state blood levels
- Allows greater control of blood levels of other AEDs
- Provides improved compliance, safety and tolerability
Significant catalysts in 2018 - 2020

SER-214 Development
- Two major indications – PD and RLS, continuous drug delivery
- RLS – enabled by current formulation; NDA 2022
- PD – wearable device for higher doses; NDA 2023
  - Combined market potential > $400 M
- SER-240 – Enter IND-enabling studies in 2019

SER-227 Development
- Post-operative pain – Prolonged analgesia, would obviate the need to discharge someone with an opioid prescription
- IND-enabling studies underway; Phase I in Q3/4-2018
  - Market potential > $1 B

SER-228/229 – POZ-cannabidiol Development
- Refractory epilepsy – IND candidate Q2-2018, Phase Ia in Q1-2019
- Myriad of potential clinical indications

SER-232 – POZ-tetrahydrocannabinol Development
- Proof-of-concept in animals in 2H-2018
Thank You