Developing a Sublingual Formulation of Apomorphine to Rapidly Convert Parkinson’s Patients from OFF to ON State

Anthony Giovinazzo
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Forward Looking Statements

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# Seasoned and Experienced Senior Management Team

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Experiences</th>
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</table>
| Anthony Giovinazzo, MBA     | President & CEO, Director                  | • 22+ years CNS experience (Parkinson’s, Alzheimer’s, Pain, Anxiety), including clinical development, IP protection and licensing  
• Extensive experience and knowledge of capital markets, institutional financing and M&A  
• MBA from IMD (Switzerland), Leadership and Strategy in Pharmaceuticals and Biotech Program (Harvard)  
• C.Dir, and A.C.C. from The Directors College |
| Dr. Thierry Bilbault, PhD   | Chief Scientific Officer & EVP CMC         | • 20+ years senior management with global large pharmaceutical companies  
• 50+ product launches internationally, including over 10 U.S. New Drug Applications; 10+ years thin film expertise  
• Held senior executive positions at Galderma, Novartis, Pfizer and Alcon Laboratories  
• MS in Biological Engineering from CUST Engineering (Clermont-Ferrand, France), and Ph.D. in Molecular and Cellular Biology from Clermont-Ferrand II (Clermont-Ferrand, France) |
| Dr. Albert Agro, PhD        | Chief Medical Officer                      | • 18+ years CNS and Parkinson’s clinical development, New Drug Applications and approvals  
• Held scientific and executive positions at TransTech Pharma, Axon, Boehringer Ingelheim and Bayer  
• Ph.D. from the Department of Medicine at McMaster University |
| Andrew Williams, MBA        | Chief Operating Officer and Chief Financial Officer | • 17+ years finance, operations and consulting, 10 yrs. working in CNS (Parkinson’s and Pain)  
• Co-founded Cynapsus in 2004; led the IPO transaction in 2006; responsible for public company operations from 2006 to present  
• BAH from Queen’s University and MBA from Richard Ivey School of Business |
Investment Highlights

• Developing APL-130277, a sublingual formulation of apomorphine to rapidly convert Parkinson's patients from OFF to ON
  - Potential to be a better alternative to approved subcutaneous apomorphine (Apokyn®)
  - 505(b)(2) pathway

• Positive Phase 2 results demonstrated rapid, clinically meaningful improvement in motor function as assessed by MDS-UPDRS Part III scores; Phase III trial underway
  - Maximum mean percent change at any time point: -45.5% for ITT and -51.3% for responders
  - ~80% of patients turned ON; mean time to full ON of 24 minutes

• Targeting a significant unmet need in Parkinson’s disease with a sizeable addressable market
  - Only company targeting all four types of OFF episodes, including morning OFF

• Experienced Management Team

• Strong cash position
Parkinson’s Disease Overview

Chronic, progressive neurodegenerative disease that results from the death of dopamine producing cells in the brain which control movement.

Oral Levodopa is the gold standard for treating the symptoms of PD, but has limitations:

- Significant variability in onset of levodopa
- Decline in response to levodopa over time
- OFF Episodes

~400,000 patients in the U.S. are in need of OFF episode treatment (1)

Addressable Market:

- 55% Mild: Treat 1 episode daily
- 25% Moderate: Treat 2 episodes daily
- 20% Advanced: Treat 3 episodes daily

*Patients that suffer OFF episodes may suffer 6 or more episodes daily

Four Types of OFF Episodes

**Morning OFF (most difficult to treat)**
- Lack of dopaminergic drugs overnight results in depleted dopamine reserves in the brain and delayed or insufficient response to first morning levodopa dose

**Delayed ON/Partial ON/Dose failure**
- Delayed ON occurs when a patient takes a dose of levodopa, but does not achieve ON in the usual time frame
- Partial ON occurs when a patient experiences some improvement in motor function but not enough to be able to perform their daily activities
- Dose failure occurs if the patient does not experience any response to levodopa

**End of Dose Wearing OFF**
- Sub-therapeutic levels of levodopa prior to next scheduled dose

**Unpredictable OFF**
- Occurs in the ON state without warning and at unexpected times

Apomorphine can effectively convert all types of OFF episodes to ON(1)

(1) Apokyn® label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021264s009lbl.pdf
OFF Episodes Broken Down Into Two Parts: Turning ON and Wearing OFF\(^{(1)}\)

*Time to ON:* the latency from taking a levodopa dose until the patient turns on

*Wearing OFF:* the time from termination of the beneficial effect of the dose until the time when the next dose is taken

\(^{(1)}\) Merims et al. *Clinical Neuropharmacol* 2003;4:196-8. Includes drug classes, approved drugs and product candidates
Benefits of Sublingual Administration

Subcutaneous Administration

- Painful to use; injection may cause scarring and injection site reactions
- Complex administration requires 15 steps
- Inconvenient
- Steep slope - blood levels can peak too quickly resulting in nausea, vomiting, and hypotension
- Indicated only for advanced patients, unpredictable OFF and dose wearing OFF

Sublingual Administration

- Painless
- Easy to use
- Convenient
- Extended half-life designed to improve efficacy
- Rounded slope lends itself to more stable ON time and a potential muting of dopaminergic adverse events
- Seeking expanded indication to include all PD patients and all OFF episodes
Lead Product APL-130277: Sublingual Apomorphine

- Turning ON medication
  - Designed to rapidly convert all types of OFF episodes to ON
- Sublingual delivery of apomorphine
  - Can be used anywhere with little or no assistance required
  - Unique bilayer avoids local irritation
- Primarily targets D1 and D2 agonists
- Dosed in 110 subjects and patients across five clinical trials
- Successfully completed Phase 2 development
- Currently being evaluated in pivotal Phase 3 trials
- Fully scaled up on a CGMP basis commercial scale equipment
Significant Unmet Medical Need Translates Into Sizeable Addressable Patient Population Looking for Convenient and Efficacious Therapy

The OFF Market is Large with Prevalence of PD Increasing

- >1mm PD patients in U.S. (1)
- 600,000 PD Patients suffer OFF episodes (2)
- Patients that suffer at least one OFF episode per day (3)

Assumptions Underlying Our Addressable Market

- Of addressable population of ~400,000 patients:
  - ~20% are considered mild (experiencing one OFF episode per day)
  - ~55% are moderate (experiencing two OFF episodes per day)
  - ~25% are advanced (experiencing three or more OFF episodes per day)

Commercialization Strategy

- ~100 targeted sales representatives will focus on high-prescribing general neurologists and ~1,200 movement disorder specialists in the U.S.
- Potential for ex-U.S. development/commercial partner(s)

- If 30% of addressable patients use APL-130277 for morning OFF, an estimated 48 million strips would be used annually
- If 50% of these patients use an additional strip daily, 72 million strips would be used annually
- If 25% use a third strip, 84 million strips would be used annually

Addressable Market (3):

- ~400K patients (~40% of PD Patients in the U.S.)

Recent Michael J. Fox Foundation Survey of 3,000 Parkinson’s patients found that 90% suffer OFF episodes and that 65% suffer at least 2 hours OFF daily

(1) CIA World Fact Book, deLau LM, Breteler MM (June 2009) “Epidemiology of Parkinson’s Disease”
(2) Rizos A et. al. “Characterizing motor and non-motor aspects of early-morning off periods in Parkinson’s disease: An international multicenter study,” 2014
(3) Estimates are based on management beliefs and publicly available research. See “Risk Factors—The market for our product candidate may not be as large as we expect”
Over the past year, we have conducted foundational research to build out a high level commercial plan for APL-130277, including preliminary sales team sizing.

Targeted Primary Research:

- OFF Market Assessment
- Competitive Assessment
- Payer Landscape and Pricing Assessment
- Physician Reactions to APL-130277

Insights Leveraged to Construct the APL-130277 Commercial Plan

- APL-130277 Product Strategy
- APL-130277 Commercial Model
- APL-130277 Commercialization Strategies
- APL-130277 Financials

Commercial investment in APL-130277 is gated to key clinical and regulatory milestones.
Summary of Clinical Trials

**CTH-103**
A single-center, Phase 1 study that evaluated the PK profile, safety and tolerability of two doses of APL-130277 compared to subcutaneous apomorphine in healthy volunteers

**CTH-105**
An open-label multicenter Phase 2 study in which APL-130277 was assessed in 19 patients with PD who experienced OFF episodes, with a total duration of at least two hours of OFF episodes daily
APL-130277 Phase 1 Clinical Trial Results (CTH-103)

• PK was comparable to SC apomorphine with rapid time to reach the minimum efficacious concentration
• Longer duration of effect compared to SC apomorphine
• More rounded Cmax than with injection
• Higher rate and severity of dopaminergic AEs with subcutaneous apomorphine compared to APL-130277
• AEs in-line with other dopamine agonists
• No severe AEs in sublingual administration arm
APL-130277 Phase 2 Clinical Trial (CTH-105)

• An open-label multi-center study in 19 patients with PD who experience at least a total duration of two hours of OFF episodes daily

• Escalating doses administered in the morning OFF state starting at 10mg up to 30mg in 5mg increments at a minimum of three hours between doses

• MDS-UPDRS Part III measured pre-dose and at 15, 30, 45, 60 and 90 minutes

• Effective dose confirmed at subsequent visit

• Patients pre-treated with antiemetic

<table>
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<tr>
<th>Baseline Demographics</th>
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<tbody>
<tr>
<td>Mean Age</td>
<td>61.5 (48-79)</td>
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<tr>
<td>Male: Female</td>
<td>14 (73.7%): 5 (26.3%)</td>
</tr>
<tr>
<td>Modified Hoehn and Yahr</td>
<td>2.2 (1-3)</td>
</tr>
<tr>
<td>Mean # of Daily OFF Episodes</td>
<td>3.9 (1-7)</td>
</tr>
<tr>
<td>Mean # of PD Medications</td>
<td>3 (1-5)</td>
</tr>
<tr>
<td>Mean Daily Levodopa Dose (mg)</td>
<td>837</td>
</tr>
<tr>
<td>Mean # of Levodopa Doses Per Day</td>
<td>5.3 (1-12)</td>
</tr>
</tbody>
</table>
**APL-130277 Positive Phase 2 Clinical Trial Results (CTH-105)**

- **Primary endpoint:** Percentage of patients who turned ON from a morning OFF state
  - 15/19 patients turned ON within 30 minutes
  - 6/15 patients turned ON within 15 minutes
  - Mean time to full ON of 24 minutes
  - 13/15 remained ON for at least 30 minutes
  - 9/15 remained ON for at least 60 minutes
  - 80% of patients turned ON with 20 mg or less

- **Secondary endpoint:** MDS-UPDRS III change from pre-dose to 15, 30, 45, 60 & 90 minutes post-dose
  - Maximum mean percent change at any time-point of -45.6% for ITT and -51.4% for responders
  - ~30% or greater improvement was seen at all time points

**APL-130277 Demonstrated a Large, Clinically Meaningful MEAN CHANGE (+/- SEM) in MDS-UPDRS Part III at All Time Points Studied**

- **ITT**
  - Intention to treat. Includes all 19 patients dosed, including 4 not dosed per protocol (2 responders and 2 non-responders)
  - Responders = 15 patients achieving a satisfactory ON, including 2 who were not dosed per protocol
  - Per Protocol = 15 patients dosed per protocol, including 13 responders and 2 non-responders

* p-value < 0.001 at all time-points
Favorable Safety Profile Demonstrated in Phase 2 (CTH-105)
Consistent with other dopamine agonists

Summary
- 19 patients; 77 doses
- Safe and well tolerated
- No apparent dose-response relationship
- No discontinuation occurred due to AEs
  - No signs of oral irritation
  - No treatment-related serious AEs

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<thead>
<tr>
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<th>Incidence of Most Common Adverse Events</th>
<th>Number of Patients</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Any AE</td>
<td>Mild AE</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (36.8)</td>
<td>7 (36.8)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>6 (31.6)</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (21.1)</td>
<td>4 (21.1)</td>
</tr>
<tr>
<td>Yawning</td>
<td>3 (15.8)</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (10.5)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>2 (10.5)</td>
<td>2 (10.5)</td>
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</table>
U.S. Regulatory Pathway

(1) Timing is based on currently available information and is subject to risks and uncertainties. See “Risk Factors” in the Company’s Form 10-Q for the quarter ended September 30, 2015 filed with the United States Securities and Exchange Commission (the “SEC”) on November 12, 2015.
APL-130277 Phase 3 Efficacy Trial Design (CTH-300)

- 12-week, randomized, double-blind, placebo controlled, study in L-Dopa responsive PD patients with "OFF" episodes
- 126 patients to be enrolled across 35 centres in North America
- Dosing: 10mg, 15mg, 20mg, 25mg, 30mg and 35mg; up to 5 doses per day
- Commenced Q2 2015; top-line data expected in the first half of 2016

**Primary endpoint:** Mean change in MDS-UPDRS Part III at 30 minutes compared to placebo at week 12

**Key secondary endpoint:** Percent of patients turning ON within 30 minutes at week 12
Bi-Layer Thin Film Dosage Form with Comprehensive Development and CMC Dossier

- APL-130277 is a patented bi-layer sublingual thin film formulated to maximize drug permeability while optimizing film disintegration properties / residence time, stability and buccal tissue compatibility
  - Apomorphine drug layer designed to provide mechanical properties to facilitate manufacturability, drug stability, rapid drug diffusion and optimal time under the tongue for desired bioavailability
  - Buffer layer ensures rapid and complete neutralization of acid generation following drug absorption while providing additional drug permeability

- CMC program encompass robust pharmaceutical development dossier including the Phase 3 clinical and registration batches produced on commercial manufacturing and packaging equipment

- Remaining CMC activities include the initiation of ICH stability studies to generate up to 12 months data at filing
IP Strategy


2nd: Protect around examples made Patent granted - USP 8,846,074

3rd: Fast track narrow claims to cover the product. Patent granted - USP 8,414,922

- Commercial protection includes broad as well as specific examples and claims

- Objective is to provide defensive protection from potential circumvention constructed by a “broad” patent application (“Sublingual Apomorphine” U.S. Patent 9,044,475 (2015) based on “Micronized apomorphine + neutralizing buffer” as the simplest defining concept

- Significant know-how required for the creation of an optimal and functional sublingual apomorphine strip system that combines key mechanical, chemical reaction and PK attributes
Financial Position\(^{(1)}\)

**Cash**
- CAD$109.5 million (USD $82.2 million)

**Share Capital**
- 12,144,622 common shares
- 3,260,954 warrants
- 973,017 options
- 16,348,593 Total (Fully Diluted)

Cash amount includes USD$72.5 million public offering (less expenses) of 5,175,000 common shares in the United States, which closed on June 23, 2015.

Stock symbols: NASDAQ (CYNA), TSX (CTH)

(1) As of September 30, 2015
Recent and Anticipated Milestones and Estimated Timeline

- **December 2015** - Posters and symposium sponsorship at the XXI World Congress on Parkinson’s Disease and Related Disorders in Milan, Italy

- **Q4 2015** - Completion of CTH-200 bridging study

- **Q4 2015** - Update on initial regulatory and clinical activities for European market registration

- **Q2 2016** - Top-line data from CTH-300 Phase 3 efficacy registration study

- **Q4 2016** - Top-line data from CTH-301 Phase 3 safety registration study

- **Q4 2016** - File New Drug Application with U.S. FDA
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