Zacks Small-Cap Research

November 26, 2013
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Cynapsus Therapeutics Inc. (V.CTH-TSX)

CYNAF – Third Quarter Financials Reported, Slight Delay in CTH-103 Top-Line Results…

Current Recommendation	**Buy**
Prior Recommendation	N/A
Date of Last Change	07/23/2012
Current Price (11/26/13)	$0.37
Target Price	**$1.25**

UPDATE

On November 21, 2013, Cynapsus reported its third quarter 2013 financial results. Losses for the quarter were $1.26 million ($0.03 per share outstanding) vs. $0.64 million in the corresponding quarter of 2012. Cash burn was $0.943 million. The company ended the quarter with $3.41 million in cash and marketable securities.

The biggest catalysts on the horizon are the expected top-line results of the CTH-103 healthy volunteer pharmacokinetic study and the initiation of U.S. bioequivalence study CTH-201. The company has announced a slight delay in the expected reporting date of results from CTH-103 to January 2014, and results from CTH-201 are now expected in Q3-2014. We maintain our Buy recommendation and look forward to the trial data as a catalyst for a major re-valuation of the shares.

SUMMARY DATA

52-Week High	**$0.48**
52-Week Low	**$0.29**
One-Year Return (%)	**N/A**
Beta	**N/A**
Average Daily Volume (sh)	**4,549**
Shares Outstanding (mil)	**39**
Market Capitalization ($mil)	**$19**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**10**
Insider Ownership (%)	**N/A**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2013 Estimate	**N/A**
P/E using 2014 Estimate	**N/A**

Risk Level	**High**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue
(In millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2012	0 A	0 A	0 A	0 A	0 A
2013	0 A	0 A	0 A	0 E	0 E
2014					0 E
2015					0 E

Earnings per Share
(EPS is operating earnings before non-recurring items)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2012	-$0.05 A	-$0.07 A	-$0.05 A	-$0.06 A	-$0.22 A
2013	-$0.07 A	-$0.03 A	-$0.03 A	-$0.03 E	-$0.14 E
2014					-$0.16 E
2015					-$0.07 E

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WHAT'S NEW



On November 21, 2013 Cynapsus (TSX-V: CTH; OTCQX: CYNAF) reported its third quarter 2013 financial results. Losses for the quarter were $1.26 million ($0.03 per share outstanding) vs. $0.64 million in the corresponding quarter of 2012. Key expenses included $0.74 million in G&A (vs. $0.21 million in the corresponding quarter of 2012) and $0.40 million in R&D expenses (vs. $0.10 million in the third quarter of 2012). The company also recorded a non-cash charge of $0.11 million in connection with employee stock-based compensation.

The increase in G&A expenses relative to the corresponding period in 2012 is primarily due to increases in senior officers' base salaries, increases in investor and public relations activities, and increases in Board retainer and meeting fees commencing July 1, 2013. The increase in R&D expense relative to the same period in 2012 reflects the net difference between Q3 2012 spending on the CTH-102 trial and Q3 2013 spending on formulation development and analytical methods development in Q3 2013. The ongoing CTH-103 trial is supported by a grant from the Michael J. Fox Foundation.

Cash used in operating activities was $0.94 million. The $0.32 million difference between operating loss and cash used in operations was mainly due to $0.11 million in share based compensation, a $0.12 million decrease in pre-paid expenses, and a $0.07 million increase in accounts payable. Cash used for investing activities was nil in the third quarter, as in the corresponding quarter of 2012. Cash generated in financing activities was nil vs. $0.1 million in the corresponding quarter of 2012. Cash and marketable securities on September 30, 2013 totaled $3.41 million, compared to $4.35 million on June 30, 2013. Net current assets at the end of the third quarter totaled $1.62 million. Current cash plus the proceeds of a $0.24 million milestone payment expected from the Michael J. Fox Foundation in the fourth quarter of 2013 appears sufficient to fund operations into the first quarter of 2014.

As of September 30, 2013, there were 38.88 common shares outstanding, 21.55 million warrants with a weighted average strike price of $0.58, and 2.69 million options with a weighted average strike price of $0.58.

The company's November 21st earnings release further disclosed that the timeline for disclosing top-line results from the CTH-103 pilot healthy volunteer study had been pushed back from the fourth quarter of 2013 to January of 2014. The timeline for the reporting of top-line results of the subsequent Bioequivalence Study (the first of two registrational studies) was pushed back from mid-2014 to Q3-2014. We assume that other, later timelines contingent upon the completion of these tasks have been pushed back slightly as well, although the delay looks minor and this does not seem to be a major concern.

We initiated coverage of Cynapsus Therapeutics Inc. (Toronto: CTH:V, OTC: CYNAF) on June 3, 2013 with a Buy rating and a $1.25 price target. We believe the company's focus on developing a sublingual form of the injectable Parkinson's drug apomorphine offers significant upside potential with a limited financial commitment, and that the company's commercial strategy to partner with a larger pharmaceutical organization presents meaningful upside to investors today.

INVESTMENT THESIS

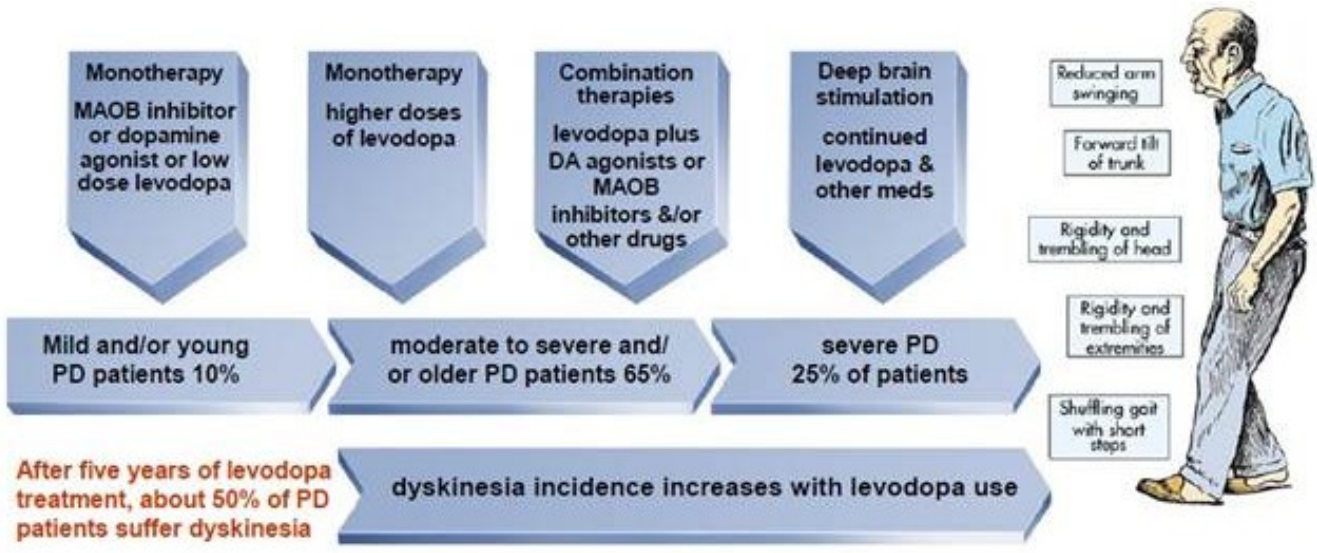
Parkinson's Disease

Parkinson's disease (PD) is a slowly progressing neurological disorder characterized by tremor, stiffness, slow and decreased movement, and postural instability affecting approximately 0.4% of the population over age 40 and 1% of those over age 65 (source: Merck Manual). The disease arises from the death of dopamine-generating cells in the substantia nigra region of the midbrain, believed by many to be in association with the accumulation of a protein called alpha-synuclein in neurons. The disease is named after the English doctor James Parkinson, who published the first detailed description in *An Essay on the Shaking Palsy* in 1817.

The earliest symptoms of the disease include tremor, typically of a single hand or foot while at rest. Tremors may become less prominent and rigidity more prominent as the disease progresses. Over time, the patient finds it more difficult to initiate movement (akinesia) and movement generally becomes slower (bradykinesia) and reduced in amplitude. Muscle pain and fatigue are common in association with these symptoms. The face eventually becomes masklike with open mouth and drooling, and speech becomes unclear and difficult to initiate. Postural instability becomes more prominent as the disease progresses, resulting in difficulty walking and maintaining balance. Without warning, voluntary movement may suddenly halt. Overall, patients with PD find it increasingly difficult to initiate and control movement as the disease progresses, leading to disability, isolation, and loss of independence. In the most advanced stages of the illness, increasing physical disability may be accompanied by a variety of other neurological symptoms, including insomnia, psychosis, and dementia.

Treatment Options

There are no disease-modifying agents available for the treatment of PD. Instead, the goal of treatment is to reduce symptoms, which can often be maintained at manageable levels for many years. In the early stages of the disease, patients may be treated with dopamine agonists such as Mirapex™, which binds to and turns on dopamine receptors in the brain in a manner closely analogous to dopamine itself. Alternatively, drugs called monoamine oxidase inhibitors may be used. Monoamine oxidase plays an important role in the healthy brain by metabolizing dopamine and preventing its level from rising excessively. However, in the Parkinson's brain inhibitors of this enzyme help offset the effect of reduced dopamine production.



As the disease progresses, treatment with MAO inhibitors or dopamine agonists are no longer sufficient to control symptoms and treatment with levodopa is initiated. Levodopa, discovered in the 1960's, is an amino acid derivative that enters the brain via specific amino acid transporters and is converted to dopamine by an enzyme called dopa decarboxylase (Hauser RA, 2009). The administration of levodopa temporarily diminishes the motor symptoms associated with the lack of dopamine in the substantia nigra. Unfortunately, only about 5-10% of L-DOPA crosses the blood-brain barrier. The remainder is often metabolized to dopamine elsewhere, causing a variety of side effects including nausea, dyskinesias, and joint stiffness.

In the 1970's, the dopamine decarboxylase inhibitor carbidopa was discovered. Carbidopa is an inhibitor of aromatic amino acid decarboxylation, an enzyme that breaks down L-Dopa in the periphery and converts it to dopamine. By inhibiting the breakdown of L-DOPA to dopamine outside of the brain, the addition of carbidopa reduces the amount of levodopa required to produce a given response by about 75% and, when administered with levodopa, increases both plasma levels and the plasma half-life of levodopa, and decreases plasma and urinary dopamine. A combination levodopa/carbidopa formulation called SINMET CR is available in the U.S. This approach helps to reduce some of the side effects of dopamine therapy, but does not slow disease progression or inhibit dyskinesia, nausea, hallucinations, and other psychiatric disorders from developing.

…Impact of off periods…

> *I am having troubles with getting my husband out of the car when he is off- he is so frozen he can't move his feet at all - so I have to lift them up, put them in correct position outside the car, and try to drag him up to a standing position---there has to be a better way!!!*
>
> **-Caretaker comment left on a Parkinson's disease message board.**

Although the initial treatment of PD with levodopa may restore motor function to normal or near normal, most patients will develop motor fluctuations within 2-5 years of initiating treatment. Symptom control may fluctuate unpredictably between effective and ineffective, with difficulty in speech and movement as the dose wears off ("off periods") and dyskinesia when drug levels are high as dose is increased in an effort to control off periods. The dyskinesias and off periods are exacerbated by levodopa's short half-life. Traditionally, the swings between dyskinesia and off periods are managed by using small doses of levodopa at intervals of as little as 1 hour, which is clearly impractical. Alternative methods to decrease the off (akinetic) times include adjunctive use of dopamine agonists, as well as COMT and/or MAO inhibitors.

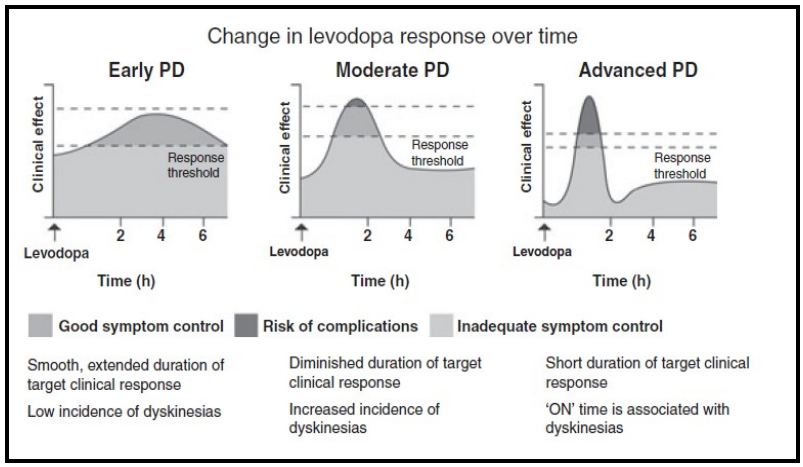
Slow or controlled release intravenous formulations of L-dopa are available, but are typically used only at night. They have not proven to have significant advantage in controlling off periods. In fact, a continuous infusion of levodopa may bring upon symptoms of dyskinesia at a greater rate than quick-release / immediate release oral formulations. With standard immediate release levodopa, levodopa-induced dyskinesia (LID) develops at a rate of approximately 10% per annum (Shapira, 2009).

Early-morning akinesia is often the first motor complication of PD, noticed by the patient, after he/she begins to awaken with symptoms of Parkinsonism after the nightlong treatment-free period. Patients with early-morning akinesia often also experience a delay in restoration of their motor function after taking their initial morning dose of levodopa. This is known as slow or delayed "ON" or latency to on. Patients may misguidedly take a higher than prescribed initial morning dose of levodopa, hoping to obtain a quicker on. Unfortunately, this can lead to dyskinesia (uncontrolled movements) and a hastening of tachyphylaxis to levodopa therapy.

End of dose wearing off is characterized by declining mobility as the dose period progresses to its end. End of dose wearing off is the most common motor fluctuation in PD and thought to be caused by a reduced duration of action of levodopa (more so than that observed with dopamine agonists). Sudden on/off fluctuations can occur at any time during the day or dose cycle. The unpredictability of sudden off is particularly disturbing to patients, causing anxiety, depression and feelings of loss of control. Dose failure or failure to achieve on refers to the absence of any clinical response to a dose of levodopa and most often occurs in patients who require frequent dosing.

Physicians often think of motor complications as mid- or later-stage manifestations of Parkinson's disease. About 40% of patients develop motor complications 4-6 years after initiation of levodopa therapy; and 70% are affected at 9 years. However, end of dose wearing off occurs in as many as 25% of patients within 6 months of the initiation of levodopa therapy and in as many as 50% within 18 months. A paper by Schapira et al in the European Journal of Neurology entitled, "Levodopa in the treatment of Parkinson's disease" (2009, 16:982-989), the authors note:

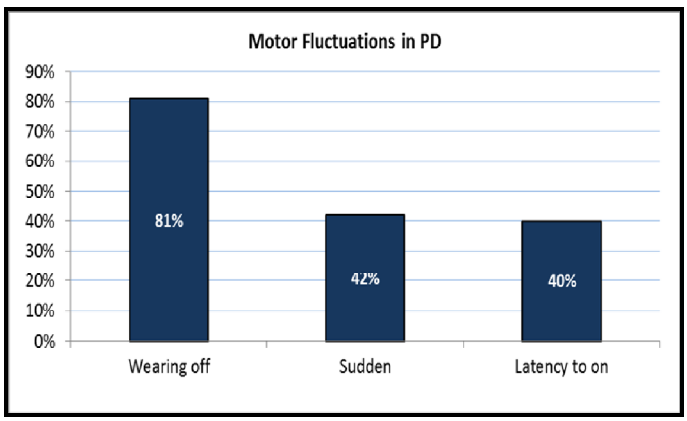
"Early Parkinson's disease is associated with a prolonged response to levodopa. Disease progression and levodopa characteristics, e.g. short half-life lead to changes that result in a shorter duration of action with wearing off of motor benefit prior to the next dose. Peak dose dyskinesias also begin to appear. As neurodegeneration advances and the adverse effects of levodopa accrue, clinical response becomes ever shorter and unpredictable with more pronounced dyskinesias."

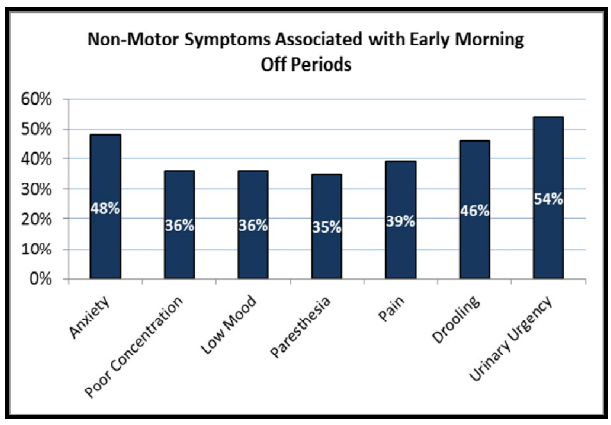


The figure to the right depicts the changing response to levodopa therapy with disease progression. Patients with advanced PD exhibit poor disease control, greater risk of off periods and on time with dyskinesias.

An observational registry, Implications of Motor Fluctuations in Parkinson's Disease Patients on Chronic Therapy (IMPACT), was established to catalog characteristics of on-off fluctuations in patients with PD who experience off periods and educate physicians to assist them in making more informed treatment decisions. Inclusion of cases in IMPACT required completion of interviews by both patients and their physicians. Both interviews were completed in 1,196 of 1,256 enrolled patients. The three most common types of fluctuation were wearing off (reported by 81%), sudden onset (42%) and latency to on (40%). The average duration of an off period was 50 minutes. The most significant quality of life problems reported by patients were loss of mobility and decreased performance in activities of daily living. Results were presented at the 9th International Congress of Parkinson's Disease and Movement Disorder in 2005.

A related, smaller study performed by the European Parkinson's Association, and published in Movement Disorders (Rizos et al, 2012) found that early morning off periods were experienced by 48% of patients with mild Parkinson's disease, 79% of patients with moderate Parkinson's disease, and 62% of patients with severe disease. Non-motor symptoms experienced by patients during their off periods included pain, urinary urgency, drooling, anxiety, and other adverse psychological effects.





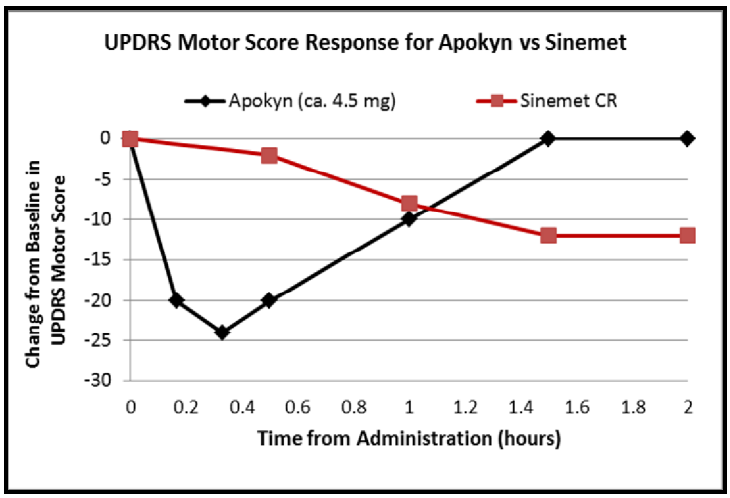
Apomorphine – A Rescue Therapy for Off Periods

Apomorphine, a non-ergot, potent dopamine agonist that binds principally to D1-like and D2-like receptors, is the only available and effective drug for acute rescue treatment that reverses the off episodes of PD. Apomorphine was first used as a PD treatment as early as 1951. Clinical use was first reported in 1970. Unfortunately, the drug's emetic properties and short half-life rendered oral use impractical. A later study found that combining apomorphine with the peripheral dopamine receptor blocker, domperidone (10 mg), improved results significantly by reducing apomorphine-induced nausea.

Apomorphine, distributed as branded Apokyn™ by Louisville, Kentucky-based U.S. WorldMeds, is administered as a subcutaneous injection. Peak serum concentrations occur 10 to 60 minutes after injection. Maximum cerebrospinal fluid concentrations are about 10% those in serum, and lag the peak serum concentration by 10 to 20 minutes. Clearance is rapid, with the serum half-life being in the range of 30 to 60 minutes.

The effectiveness of Apokyn in the acute symptomatic treatment of the recurring episodes of hypomobility, “off” episodes (“end-of-dose wearing off” and unpredictable “on/off” episodes), associated with advanced Parkinson’s disease was established in three randomized, controlled trials. On average, patients participating in these trials had Parkinson’s disease for 11.3 years and were being treated with L-dopa and at least one other agent, usually an oral dopamine agonist. One of the three studies was conducted in patients who did not have prior exposure to apomorphine and two were conducted in patients with at least 3 months of apomorphine use immediately prior to study enrollment.

The Figure to the right shows the improvement in Unified Parkinson’s Disease Rating Scale (UPDRS) motor score obtained by patients as a function of time after injection of apomorphine. Patients in the active treatment arm achieved a peak -24 point change in mean UPDRS motor score within 20 minutes of dosing.



The UPDRS motor score is a 64 clinician rated scale measuring speech, facial expression, tremor at rest, tremor, rigidity, posture, postural stability, overall bradykinesia and akinesia, and ability to perform simple motor tasks such as hand movements, finger tapping, leg movements, arising from a chair. A change of 5 points is considered clinically significant (Schrag et al, 2006).

The 20 minute mean time to maximum response after an injection of apomorphine can be compared with an approximately 2-3 hour mean time to maximum response after oral administration of Sinemet-CR (Piccini et al, 2000). These data were obtained in two unrelated studies performed in different patient populations. The absolute value of the UPDRS change is probably not comparable across the two studies, but the graph shows that approximately 1.5 hours is needed to obtain maximum effect with Sinemet CR vs. about 20 minutes for Apokyn. The onset of activity is somewhat faster for the immediate release form of Sinemet, but it is not widely used. Therefore, we conclude that adjunct apomorphine can be an effective compliment to Sinemet-CR therapy, filling the gaps between Sinemet doses when “wearing off” or risk of “sudden off” occurs.

Among the most common adverse events associated with apomorphine treatment are nausea and vomiting. Since apomorphine is emetic, in clinical studies, patients received an anti-emetic agent, trimethobenzamide, for three days prior to beginning apomorphine and encouraged to continue trimethobenzamide for at least 6 weeks. In clinical trials, among 522 patients treated, 262 (50%) discontinued trimethobenzamide while continuing apomorphine. The average time to discontinuation of trimethobenzamide was about 2 months (range: 1 day to 33 months). For the 262 patients who discontinued trimethobenzamide, 249 patients continued apomorphine without trimethobenzamide for a duration of follow-up that averaged 1 year (range: 0-3 years). However, even with the use of trimethobenzamide in clinical trials, 31% of the patients experienced nausea and 11% of the patients experienced vomiting. In clinical trials, 3% of the patients discontinued apomorphine due to nausea and 2% discontinued due to vomiting.

Experience shows that postural hypotension may affect approximately 15% of patients treated with apomorphine. Affected patients are identified and managed in higher risk groups. The total daily dose of apomorphine can range up to 20 – 25 mg / daily. During clinical development, hallucinations were reported by 14% of the patients. In one randomized, double-blind, placebo-controlled study, hallucinations or confusion occurred in 10% of patients treated with Apokyn compared to 0% of patients treated with placebo. Hallucinations resulted in discontinuation of apomorphine in about 1% of patients.

Subcutaneous (SC) apomorphine has been available in Europe for the intermittent treatment of off periods of PD since 1993, was approved in the U.S. in April 2004. The US FDA approval is for Apokyn (apomorphine hydrochloride injection; Britannia Pharmaceuticals Ltd.), which is indicated for the acute, intermittent treatment of hypomobility, off episodes (end-of-dose wearing off and unpredictable on/off episodes) associated with advanced Parkinson's disease

…Limitations of Apomorphine SC Injection…

Injectable products are normally unpopular with patients due to the expected issues of needle phobia, injection site pain / reactions, and the simple inconvenience of carrying a syringe and vial of liquid drug when outside the home. In the case of patients with Parkinson disease, the unattractiveness of injectable apomorphine is greatly magnified by the fact that it requires mechanical dexterity at precisely the moment when the patient is experiencing a crisis in their ability to initiate and control their movement. We also note that Apokyn subcutaneous injection is a hydrochloride solution and some patients have complained about a burning sensation or injection-site reactions with use of the product. According to the Apokyn label, 26% of patients complain of injection site reactions, with the most common being bruising (16%), granuloma (4%), and pruritis (2%). These issues are surely an important part of the explanation for why combined U.S. and EU apomorphine sales have run at or below $10 million in recent years. We see SC Apokyn as efficacious drug, but with a terrible delivery.

Attempts to develop an oral formulation of apomorphine have been stymied because oral (swallowed) apomorphine is not absorbed into systemic circulation. Drugs taken by the oral route enter the bloodstream by crossing the intestinal epithelia into capillaries that feed the portal vein. Blood from the portal vein passes through the liver before traveling back to the heart, and then onto the other organs. Because the liver is the main organ in which drug metabolizing enzymes are found, easily metabolized drugs such as apomorphine undergo what is called first pass metabolism. This means that drug absorbed from the intestine is completely metabolized while passing through the liver, and never appears in the general circulation.

A few companies have attempted to develop alternative formulations of apomorphine. Takeda-Abbott Labs developed a low-dose sublingual apomorphine product called Uprima for erectile dysfunction. Clinical trials studying high-dose Uprima for the treatment of Parkinson's disease was stymied and eventually discontinued because of poor bioavailability and long "lag-to-onset" of action. We note back when Takeda-Abbott attempted to develop this product, sublingual film formulations where not yet perfected. Cynapsus sublingual film formulation provides better absorption and onset than the sublingual tablet previously developed by Takeda-Abbott. Amarin Pharmaceuticals was developing a sublingual liquid formulation of apomorphine, but the product had to be extemporaneously mixed with a liquid neutralizing buffer prior to dosing and applied under the tongue with a syringe. It was rather impractical and thus discontinued.

Several companies were previously working on nasal delivery formulations of apomorphine to no avail. West Pharmaceuticals, Nastech, and Brittania had an intra-nasal apomorphine product that failed due to irritation of the nasal passages, and Archimedes Pharmaceuticals had a nasal delivery formulation that failed due to poor absorption and irritation. Vectura Pharmaceuticals is developing a pulmonary delivery device for powder inhalation of apomorphine. The PK profile shows very rapid absorption of apomorphine, but the product failed to show statistical significance on efficacy. We note the FDA has been wary of systemic delivery via the pulmonary route which can lead to reduction in lung capacity. These are unique safety concerns of the inhaled route that will require extensive clinical demonstrations.

We note that when approved in 2004, Apokyn was granted Orphan Drug designation by the U.S. FDA. The label included use for only severe patients as a rescue therapy, and thus the patient population qualified for the benefits of Orphan status. The seven-year market exclusivity on Apokyn prevented companies from seeking the 505(b)(2) pathway noted above by Cynapsus. This exclusivity expired in 2011. Cynapsus recently received a patent for its sublingual film product of apomorphine, securing the first-mover advantage in this now wide open market.

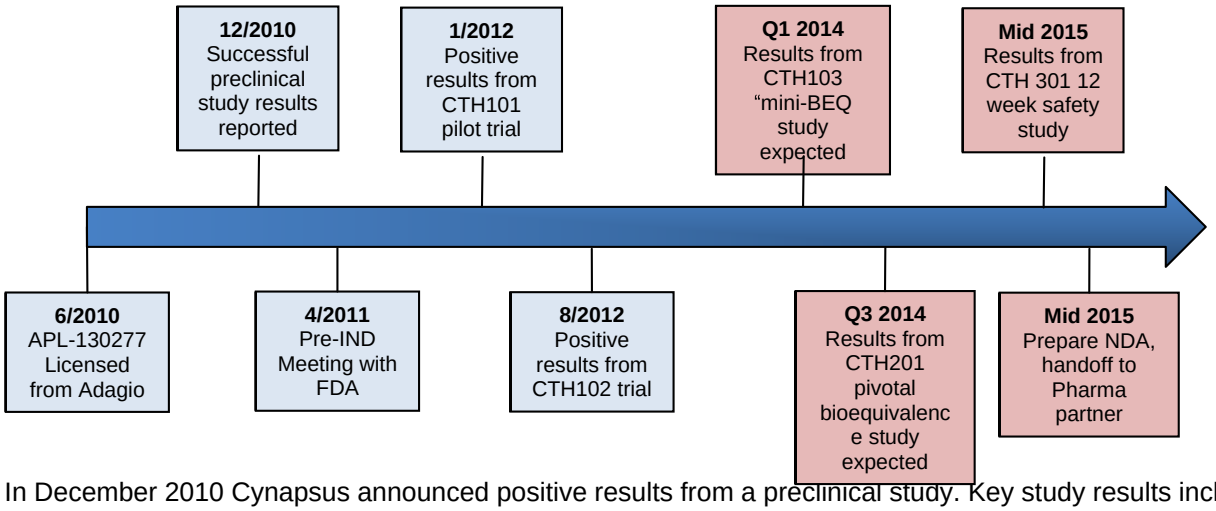
The Cynapsus Sublingual Formulation

Cynapsus is developing APL-130277, a fast-dissolving, fast-acting thin film formulation of apomorphine that can be administered in the mouth. In this route of administration, the drug is absorbed into the bloodstream by diffusing through the tissues of the mouth. The formulation technology for sublingual (SL) drug administration is well developed, and has previously been successfully applied other drugs that undergo rapid first pass metabolism and / or for which rapid absorption into the bloodstream is required. Examples include Abstral® (fentanyl), Suboxone® (buprenorphine/naloxone), Zuplenz® (ondansetron), Saphris® (asenapine), Intermezzo® (zolpidem), and Striant® (testosterone).

Advantages of SL film formulation are expected to include greater ease of self-administration by patients experiencing off-episodes, greater convenience in addressing off episodes that occur outside the home, and reduced side effects of self-injection including irritation, pain, nodule formation, panniculitis, inflammation, infection, and scarring. Cynapsus believes that the convenience, ease of use, comfort, and safety of SL APL-130277 will allow its use not only in the later stage PD, but in milder forms as well thus expanding the current market for the drug. Cynapsus believes that by including APL-130277 earlier into the treatment paradigm, patients could improve symptom management and outcomes, such a reduction in levodopa requirements (levodopa-sparing), which in turn could slow the rate of wearing-off observed with levodopa monotherapy.

…Regulatory Pathway…

The company is pursuing an expedited regulatory pathway for APL-130277 that avoids the need for large efficacy trials by developing a sublingual formulation that closely mimics the pharmacokinetic profile of the approved subcutaneous formulation of apomorphine. In April 2011 the FDA confirmed that Cynapsus may rely on safety and efficacy data from the prior submission on Apokyn (apomorphine hydrochloride injection) and that Cynapsus can pursue a 505(b)(2) submission with APL-130277, based on (1) a demonstration of pharmacokinetic bioequivalence and T_{max} that is similar to that claimed in the Apokyn label, and (2) a demonstration of good safety and local tolerance as relates to the new sublingual route of administration of the drug.



In December 2010 Cynapsus announced positive results from a preclinical study. Key study results included

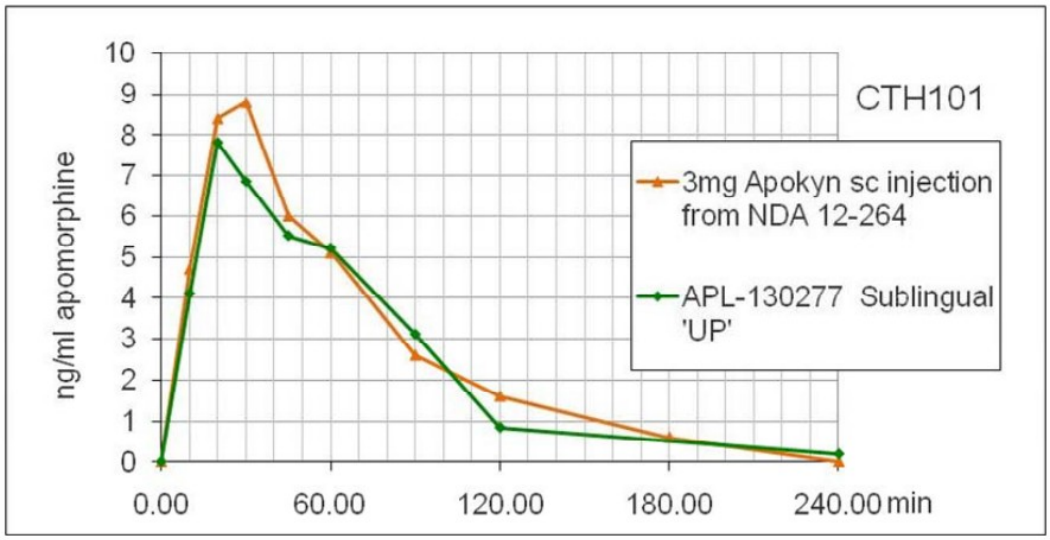
- ✓ Demonstration that the thin-strip prototypes dissolve rapidly under the tongue in a reasonable amount of time, achieving the targeted T_{max}.
- ✓ Demonstration that the prototypes deliver drug to the bloodstream in appropriate amounts and at an appropriate rate to achieve the targeted AUC and C_{max}. The study demonstrated that the strips have a similar pharmacokinetic profile to subcutaneously injected apomorphine

In April 2011, the company had a pre-IND meeting with U.S. FDA. Cynapsus reviewed the drug product concept, data obtained to date and proposed a 505(b)(2) type regulatory pathway for approval of APL-130227. As described in minutes from that meeting, the FDA agreed that a demonstration of bioequivalence of APL-130277 to Apokyn subcutaneous injection would provide sufficient proof of PK equivalence of the new drug product.

Bioequivalence traditionally demonstrated via a phase 1 pharmacokinetic clinical study where serum levels of a single dose of a test product are compared to a single dose of approved (reference) drug in an appropriately designed crossover study using healthy human volunteers. Statistical analysis of the maximum serum level (C_{max}) and the total exposure, as measured by the area under the curve (AUC) should be between 80% and 125% with a confidence interval of 95%.

In addition, the FDA will require an additional study in naïve Parkinson's patients over a minimum of 12 weeks to demonstrate safety and tolerability of the drug that is administered via this new route of administration. Our understanding from conversations with management is that as long as the company does not stray from the Apokyn label, with demonstrated bioequivalence, approval should be relatively straightforward. Straying from the approved label, (e.g. what Transcept did with Intermezzo vs. zolpidem) creates risk to the application and the potential for a complete response letter.

In January 2012, Cynapsus announced positive data from the first human volunteer pilot proof-of-concept study (CTH-101) of APL-130277. The PK and safety / tolerability of APL-130277 were demonstrated in 15 healthy volunteers with 12 of 15 subjects receiving drug product and 3 subjects receiving placebo. Patients were dosed in a two period crossover with APL-130277 placing the drug in a different orientation under the tongue.



Major findings from the study included.

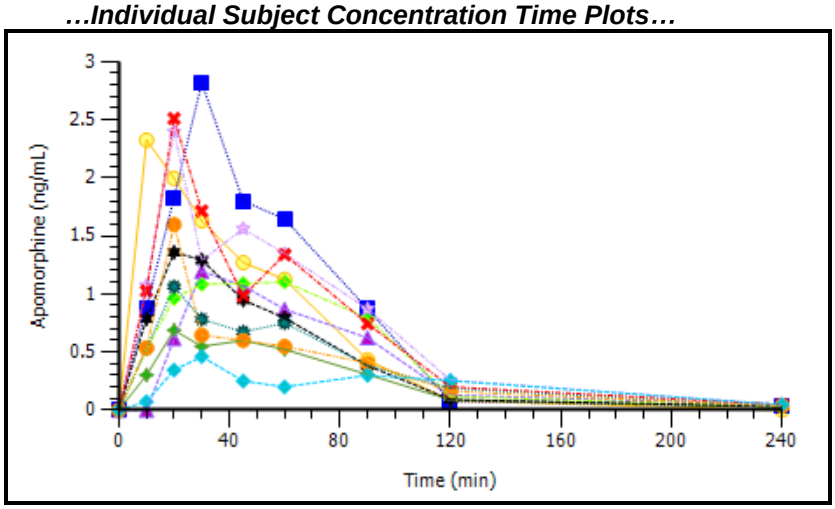
- ✓ Pharmacokinetic parameters mirrored those seen with a subcutaneous injection of apomorphine after an expected dose adjustment. As measured by C_{max} and AUC, the dose administered by the original 3 mg version of the strip was only about 15% that delivered by 3 mg apomorphine subcutaneous injection.

- ✓ The necessary upward adjustment in dose was discussed with the strip manufacturer who advised that the 17 mg dose required to mimic the exposure profile of a 3 mg injection was technically feasible.

- ✓ The orientation of the strip under the tongue impacted the rate of apomorphine appearance in the blood stream, with more rapid release occurring when the drug-containing face of the strip faced downward.

- ✓ Inter-patient variability in C_{max} and AUC were somewhat greater than historically observed with subcutaneously administered apomorphine (see chart below for 14 patients). The coefficients of variation for C_{max} and AUC were 48% and 34% respectively, compared to the average historical values of 30% and 24% for Apokyn (based on package insert). However, we note the company has conducted a second study (CTH-102) vastly improved pharmacokinetics with a new formulation (29% coefficient of variation for C_{max} and 27% for AUC. This data compared well with the subcutaneous delivery.

…Individual Subject Concentration Time Plots…



- ✓ APL-130277 was safe and with no local irritation or tolerability issues. Adverse event rates were similar to those seen historically with subcutaneous apomorphine.

- ✓ Certain minor problems with the prototype product were identified. Some patients objected to the strong menthol taste of the original formulation, and the administering pharmacist noted that the prototype was tacky and difficult to lay flat.

In August 2012, Cynapsus announced the results of a second human volunteer pilot proof-of-concept clinical trial (CTH-102) of APL-130277. The goals of this trial were in part to identify the correct dose of sublingual apomorphine to best reproduce the pharmacokinetic profile of 3 mg Apokyn injection. The trial enrolled 15 patients, of whom 12 received active drug and 3 received placebo. This trial employed a refined formulation of the sublingual film, controlled for the orientation of the film within the patients' mouth, and exercised greater control over clinical and analytical profiles.

- ✓ The trial was stopped after the first dose examined was judged to adequately reproduce the pharmacokinetic (C_{max}, AUC and T_{max}) profile of subcutaneous apomorphine.

- ✓ The observed T_{max} was 40 minutes. The data showed reduced variability relative to the CTH-101 study (as noted above).

- ✓ Adverse events were similar to those historically observed with subcutaneous apomorphine.

Based in part of these results, the company began preparations for CTH-103, three dose, active comparator, placebo-controlled, randomized cross-over bioequivalence phase I trial comparing APL-130277 to subcutaneous apomorphine. The trial will enroll 48 subjects in 3 cohorts. Patients within each cohort will receive either APL-130277 or subcutaneous apomorphine in random order. Following a 1 day washout period, they will then cross over to the drug not administered on Day 1.

- → Cohort 1 will be administered either 10 mg APL-130277 or 2 mg subcutaneous apomorphine
- → Cohort 2 will be administered either 15 mg APL-130277 or 3 mg subcutaneous apomorphine
- → Cohort 3 will be administered either 25 mg APL-130277 or 4 mg subcutaneous apomorphine

Study endpoints include a complete pharmacokinetic profile with comparisons to subcutaneous apomorphine data, and safety and tolerability. The study is funded by a $0.948 million grant from the Micheal J. Fox Foundation (MJFF) and will serve as a "dry run" for the larger pivotal bioequivalence trial, CTH-201, to be performed in early 2014.

Bioequivalence, as per Cynapsus' meeting with the US FDA will be assessed based on achieving 80% to 125% with 95% confidence intervals, of the C_{max} and AUC of the injection. In addition, because the label identifies the injection as an acute rescue therapy, T_{max} will also be taken into account as discussed with the FDA. The label for the injection identifies the T_{max} range as 10 minutes to 60 minutes, with a mean of 20 minutes. As agreed to with the FDA, Cynapsus will also complete a safety and tolerability study in patients with PD who have not been previously exposed to apomorphine. CTH-301 is planned to be a 3-arm study in 150 patients, with duration of 16-weeks.

…Market Potential…

In December 2011, the company reported the results of a marketing study performed by MedaCorp. The survey included a total of 500 neurologists and movement disorder specialists in the United States, Europe, Japan, China and select countries in the rest of the world. Collectively, these professionals treat approximately 62,000 Parkinson's patients per year with approximately 41.4% classified as mild-moderate in severity, 42.2% as moderate-severe, and 16.4% as severe. Key results of the survey included:

- Neurologists view needle injection of apomorphine as an important barrier to expanded use. According to the survey, neurologists and movement disorder specialists prescribe Apomorphine by needle injection or infusion pump to approximately 5% of all Parkinson's patients. Among these patients, they describe 6.4% as mild-moderate patients, 40.2% as moderate-severe patients, and 53.4% as severe. In addition, survey respondents reported that "inconvenience", "difficulty starting therapy" and "injection-site reactions" as the biggest barriers preventing them from expanding use to a broader spectrum of PD patients.

- Estimated use of sublingual Apomorphine (such as APL 130277). If a sublingual, solid, fast-dissolving dosage form of Apomorphine was made available (such as APL 130277), respondents would consider using the drug in 15.1% of mild-moderate patients, 38.1% of moderate-severe patients, and 49.5% of severe Parkinson's patients. Taking into account the classification of patients (i.e. mild-moderate, moderate-severe, severe), these projected uses would represent approximately 30% of all Parkinson's patients, or around a 6-fold increase in use.

- Neurologists would be willing to prescribe sublingual apomorphine at launch. One year post launch, respondents reported that they would expect to treat 13.2% of mild-moderate, 22.9% of moderate-severe, and 26.0% of severe patients with sublingual apomorphine. The survey also showed that the United States is particularly ready to accept innovation, as initial adoption rates are shown to be two times higher in the United States than in Europe or the rest of the world.

Besides surveying neurologists and movement disorder specialists, the company also spoke with 11 large U.S. payers (HMO and insurers). Results of the survey show a potential very favorable pricing environment and high acceptance for reimbursement. The results show that 90% of the responders would reimburse the product within three months of approval by the FDA. Roughly 75% of the responders would reimburse at an average wholesale price equal to the apomorphine injection, with another 50% amenable to a premium price of 25% if the company can show clinical benefit over the injectable product.

Based on these data and the results of a payor and reimbursement survey finding that most insurers would reimburse sublingual apomorphine at the same rate as subcutaneous apomorphine (AWP of $10 per administration), the company believes that APL-130277 could be used in 48K patients in the US, a similar number in the European Union, and roughly 24K in the rest of the world. Assuming 1 administration per day for mild patients, 2 administrations per day in moderate patients and 3 in severe patients, at $7 per dose (the company is using a lower AWP price to be conservative in its forecasts), the company sees peak sales of APL-130277 at around $284 million per year in the U.S. and $712 million worldwide. With increased market penetration, the company thinks APL-130277 could be a $1.1 billion or higher drug, worldwide.

…Cynapsus Internal Projections…

	US
Diagnosed and Treated	411K*

*Conservative estimate given that American Parkinson's Association estimates 1 M patients in US today and does not take into account 2x increase over next 10 years

Segment	# of Patients	% Addressable	# Of Patients To Be Treated	Assume 50% Actual
Moderate (42%)	172K	38%	65K	32.5K
Severe (16%)	65K	49%	31K	15.5K
	237K		96K	48K

US	EU (Same as US)	RofW (1/2 US)	Total WW #
48K	48K	24K	120K

	Total # of Patients WW	Doses/Day @ $ 7/ dose	Potential WW Revenue Per Year
Moderate	81.25K	2	$ 415M
Severe	38.75K	3	$ 297M
	120k		$ 712M

	Minimal	Probable	Potential
3rd Yr Sales	$ 532	$ 729	$ 1,166
5th Yr Sales	$ 619	$ 847	$ 1,391
Peak Sales (Millions)	$ 863	$ 1,146	$ 1,941
Market Penetration % @ Peak	6.7 %	12.9 %	21.7 %
Number of Doses Per Day			
Mild	1	1	1
Moderate	2	2	2
Severe	3	3	3

Our Analysis

Cynapsus is a single asset company that seeks to develop and rapidly out-license its sublingual apomorphine product at the pre-NDA stage. Successful implementation of the company's strategy hinges upon successful execution of its regulatory strategy and potential licensees' perception of the potential market size.

With respect to the market size, we believe that the company's estimates may modestly over-estimate actual revenue potential for APL-130277 by taking the preferences of neurologists and movement disorder specialists at face-value, and not discounting the responses for actual real-world use of the drug. It is one thing for a neurologist to respond to a survey and note preference to potential use of the drug. It is another to actually write the prescription, have the patient fill that prescription, and then use the drug at the same level as described in the survey or even listed on the label. We think generating high physician awareness and education around APL-130277 will be key for driving sales once approved.

…Regulatory Strategy…

Cynapsus is pursuing a strategy of obtaining FDA approval for its sublingual apomorphine film by demonstrating bioequivalence to the approved subcutaneous apomorphine injection, Apokyn. This strategy offers the potential to minimize clinical trial expenses and risks, because a much smaller population and shorter trial design can be used to demonstrate bioequivalence relative to what would be required to demonstrate efficacy. We think, and have confirmed with management, that as long as the company does not attempt to stray from the Apokyn label, the regulatory pathway for APL-130277 is relatively straightforward. We contrast that with the strategy of Transcept Pharmaceuticals' Intermezzo, a sublingual formulation of Sanofi's Ambien (zolpidem), which was met with two complete response letters, one in October 2009 and another in July 2011, because Transcept changed the indication of use around zolpidem.

Historical data for the successful development of some sublingual formulations of drugs previously approved as oral (swallowed) or subcutaneous formulations is summarized in the table below. In some cases these formulations were approved based on the lack of oral bioavailability of the drug active substance, and in others because it was thought desirable to develop a formulation that was more rapidly absorbed or that was more appropriate for patients who have difficulty swallowing.

Among these representative examples, we identified only a single case in which a sublingual formulation was approved based on the demonstration of bioequivalence to a predicate product in which the active ingredient is administered by a completely different route. In most cases, approval was based on the demonstration of efficacy of the new formulation and route of administration. We hypothesize that this may be due to the difficulty of optimizing the sublingual formulation against multiple endpoints, including both the mean values and standard deviations of time to maximum serum concentrations (T_{max}), maximum serum concentration (C_{max}), and total drug exposure (AUC or area under the curve). However, more likely is that the company seeking approval for the sublingual formulation altered the indication for use, such as Intermezzo for middle-of-the-night insomnia or Actiq for abuse deterance.

Table. Representative approved sublingual drugs

Sublingual Formulation	Active Ingredient	505(b)2 Predicate Drug	Developmental Rationale and Pivotal Trials
Zuplenz®	Odansetron	Zofran®ODT	Approved via 505(b)2 based on demonstration of bioequivalence to Zofran® orally disintegrating tablets in 46 patients. Zofran ODT was in turn approved based on bioequivalence to Zofran oral tablets.
Actiq®	Fentanyl	IV Fentanyl	Approval based on demonstration of efficacy in treatment of cancer pain in 275 patients and by 505(b)2 reference to IV fentanyl. Previously available only by IV infusion.
Intermezzo®	Zolpidem	Ambien®	Designed to increase speed of absorption and onset of effect relative to oral predicate drug Ambien. Approved based on 505(b)2 reference to Ambien and efficacy studies in 377 patients.
Suboxone®	Buprenorphine and naloxone	NA	Buprenorphine has poor oral bioavailability. Approved based on efficacy in treatment of addiction in 575 patients.
Striant®	Testosterone	NA	Testosterone is not orally available due to rapid first pass metabolism in the liver. Approved based on efficacy studies in 127 men with primary endpoint of maintenance of testosterone levels within normal physiological range.
Saphris®	Asenapine	NA	Sublingual formulation of asenapine, approved based on efficacy studies in 622 patients. There was no previously approved product containing the active ingredient asenapine, which exhibits poor oral bioavailability

That said, the mean drug plasma levels over time observed in table below appear very promising with respect to Cynapsus' ability to meet the FDA's requirement that the C_{max} and AUC of APL-130277 lie between 80% and 125% of that of Apokyn. We note a modest concern that the standard deviations of these parameters observed in CTH-101 were nearly twice as large as those recorded historically for subcutaneous apomorphine, but remind investors this was prior to the follow-up CTH102 study to identify the correct dose. Plus, Cynapsus is not attempting to change the indication for use. The company is looking to expand into more mild-to-moderate patients, but the indication of APL-130277 will be identical to Apokyn, and that dramatically lowers regulatory risk, in our opinion.

…Zacks Market Forecasts…

Risk to the company's projection of APL-130277 as a $600 million to $1 billion drug stems from the addressable market size estimate provided by Cynapsus' neurologist survey, and by the studies of OFF episode prevalence described above that may overestimate actual revenues as they address neurologist's willingness to prescribe, but not the patient's willingness to use sublingual apomorphine.

If the assumptions that the difficulty of administration and injection related pain are the main barriers to apomorphine uptake, then Cynapsus' market estimates will be reasonably accurate. However, if there are other reasons for the poor uptake of apomorphine, such as effectiveness, variability and reliability of effect, or side-effects, which may not be addressed by a sublingual formulation of the drug, utilization and revenues could be substantially lower. We remind investors that Apokyn U.S. sales are only around $10 million per year, and around $50 million worldwide.

Patients clearly prefer oral over self-injected medications. In the case of Parkinson's disease, this preference is likely to be even stronger because of the requirement for physical dexterity in performing the injection, and the fact that the need for medication occurs precisely when patient is having trouble moving. But a key question to ask, "Is all of the limited use of Apokyn attributed solely to its method of delivery?"

To evaluate this question, we undertook an admittedly unscientific and potentially unrepresentative survey of patient comments about Apokyn on Parkinson's disease support websites and other websites on which such comments may be found. Representative samples of positive comments are shown in the PRO-Table and of negative comments in CON-Table below.

PRO-TABLE

".. it is a miracle I can inject it and within 10-15 minutes I get up and go. I work full time…"	Parkinsonsmovement.health.com
"We can cook food, give him a shot and in a couple of minutes he can get himself out of the chair and eat his dinner. He should have been on this years' ago. It is a miracle medicine."	www.drugs.com
"There are times when the meds don't even kick in for an hour. In spring of 2012, he was prescribed Apokyn (injectable dopamine). It really does the trick and jump starts him."	Forum.parkinson.org
"I'm plagued with "Off Dystonias" for which in "emergency" I (or a friend) inject Apokyn which makes me good to go in 6 mins, though it causes "brain fog" 10 mins after injection"	www.dailystrength.org
"Self-injection is really a piece of cake, doesn't hurt one bit (and this is from a guy who used to get big time butterflies when drawing blood) and is over in a few seconds."	Neurotalk.psychcentral.com
"It works very quickly and is most helpful when he freezes out in public. It generally works in a matter of minutes. He has been using it for several years and doesn't seem to be as effective now as it was at first"	Forum.parkinson.org
"I am functioning at a higher level than I have been in years. In my experience Apokyn is quick acting and reliable."	Forum.parkinson.com

CON-TABLE

"We tried Apokyn. The first administration was not tolerated well. Her blood pressure dropped severely and it took over 1 hour for it to get back to normal. She then was tired the rest of the day. "	Forum.parkinson.org
"About a year ago they also tried an injection of Apokyn. For several moments there was dramatic improvement, but then his blood pressure fell very low, very rapidly and they decided not to continue."	Forum.parkinson.org
"My husband just started on Apokyn May 24. It has worked somewhat for him."	Forum.parkinson.org
" Have tried the Apokyn pen and it was a flop imho as far as a rescue medicine"	Neurotalk.psychcentral.com
"I also tried Tacapone but it didn't work much. The Apokyn, not either."	Healingwell.com
"Good to have nearby for "freezes", but really don't like giving injections."	www.drugs.com
"This medicine works great as a rescue drug although the delivery system is difficult to use."	www.drugs.com

Positive comments generally center on the rapid onset of activity of the drug, and in particular the utility of the drug in unexpected OFF episodes such as might occur when in public or preparing to go out. Negative comments seemed to break out into three approximately equally sized categories

1. **Fear of injection and difficulty of administration**. This is the problem that the sublingual formulation is intended to address

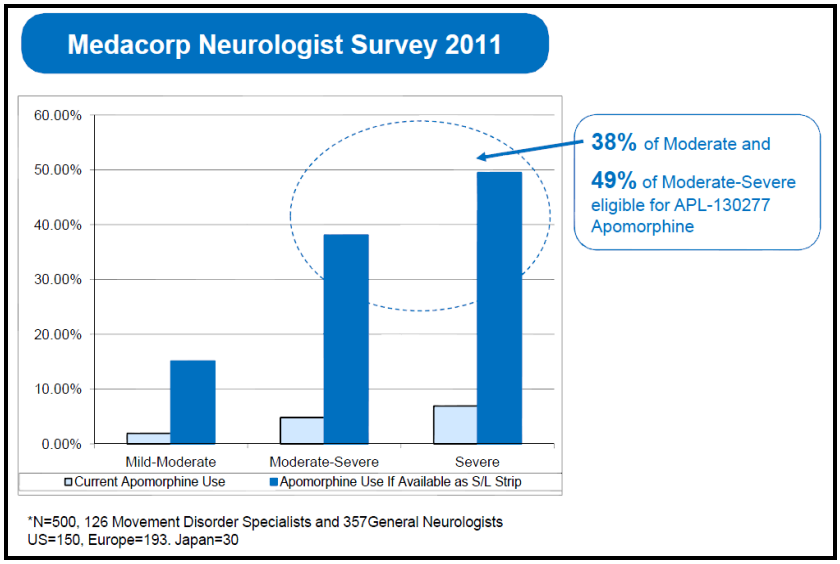
2. **Lack of efficacy**. These patient comments were mirrored by neurologists on the patient support sites (comments not shown), who emphasized that Apokyn is not a "miracle drug" and that Parkinson's therapy needs to be individually optimized for each patient. As noted in the section above, the pharmacokinetic properties of injected apomorphine are highly variable and the relationship between apomorphine's efficacy and plasma level is exceptionally steep. Numerous published studies have confirmed that inter-patient variability is much higher than intra-patient variability, thus accounting for the observation that Apokyn "doesn't work" in some patients (Gauncher ST et al, 1993). Whether inter-patient variability will also be high with the sublingual formulation remains to be seen.

3. **Adverse effects**. Dramatic blood pressure drops were cited very commonly, as was nausea. According to some patients their doctor administered their first dose in office and kept them under observation for an hour post-dose, a practice that would entail considerable inconvenience to prescribing physicians if practiced widely.

4. **Lack of compelling medical need**. While not mentioned specifically in patient online commentary, the highly variable pharmacokinetics of Apokyn may be such that many of those who do get a benefit may not find it clinically significant enough to offset drug co-pays and the unpleasantness of injection.

On a global basis, injectable apomorphine is around a $50 million product. We are unaware of any drug that has experienced a 50x to 100x increase in utilization upon the availability of a more convenient dosing form. This might suggest that the $600 million to $1 billion range for APL-130277 is too high. There have been examples of where sales of a product saw a greater-than 15x increase in sales moving from injectable to oral / sublingual (Glaxo's Imitrex). We think this is fair, and perhaps given the nature (or state) of the Parkinson's patient, even a 20-25x increase seems within reason.

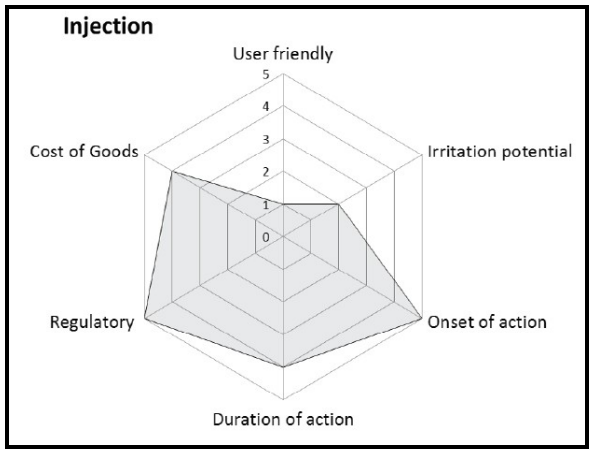
Below we post a snap-shot of our model for the ramp of APL-130277 in the U.S. We start with approximately 1 million Parkinson's disease patients, about 50% of which have significant enough "OFF" issues to where they seek or require a rescue medication such as apomorphine (Espay AJ, 2010). According to management's survey of over 500 neurologists and movement disorder specialists, the market breaks down as: ~50% with mild Parkinson's disease (might require 1 SL film per day), ~45% with moderate Parkinson's disease (might require 2 SL films per day), and ~15% with severe Parkinson's disease (might require 3 SL films per day).

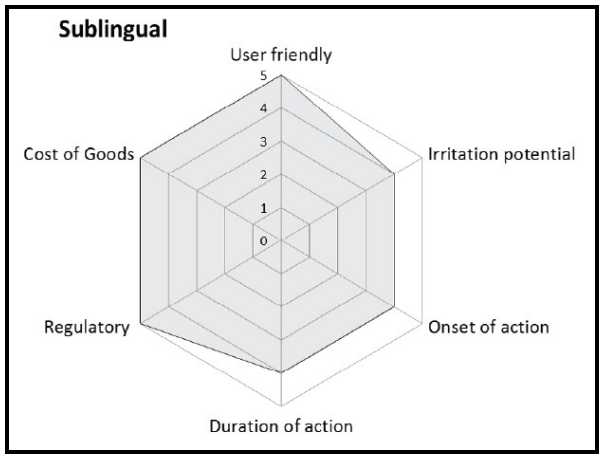


The MedaCorp survey that the company completed in late 2012 showed very strong potential uptake of a SL formulation of apomorphine, with neurologists and movement disorder specialists noting a desire to increase use by as much as 6-to-8 fold for moderate and severe patient. This suggests an increase in U.S. sales from around $10 million per year today, to around $60-80 million per year.

However, we note the limitations on the injectable not only limit the number of patients that use the product, but also how frequently those patients using the product actually take the medication. We see the SL film allowing for at least 2-3 fold increase in use on patients vs. the SC.

Below is representation of a patient favorability assessment conducted by the company and published in April 2012 issue of the Journal of Commercial Biotechnology (Volume 18 / No. 3). The company found that a sublingual formulation of apomorphine would be significantly more user friendly and less painful (scale: 1 least – 5 most friendly). As noted above, we believe not only does the sublingual formulation open up the market to an enormous number of new patients, but it expands the use per patient by as much as 2-3 fold per day.





We also assume that APL-130277 will be launched at slight discount to the injectable apomorphine, which is roughly $10 per use, to drive market share gains early in the launch. The company's survey from late 2012 provided great insight into the payor and reimbursement market for the product. The results show that 90% of the responders would reimburse the product within three months of approval by the FDA. Roughly 75% of the responders would reimburse at an average wholesale price equal to the apomorphine injection, with another 50% amenable to a premium price of 25% if the company can show clinical benefit over the injectable product.

We believe that market share penetration for APL-130277 could approach 5% for the moderate-to-severe patient population. We even see it obtainable to achieve market share in the 2.5% range with mild patients. Running these numbers suggests that APL-130277 has peak U.S. sales in the range of $200 million. Outside the U.S., the number of Parkinson's patients is another 3.0 million between Europe and Asia / Pacific. This is suggestive of a peak sales opportunity at around $600 million Ex-U.S. However, two reasons lead us to believe that sales of APL-130277 outside the U.S. may not reach this level. Standard of care outside the U.S., especially in Eastern Europe or throughout parts of Asia, falls short of ideal, and as such use and familiarity with apomorphine is not nearly as high as in the U.S. Pricing power (or ability to gain reimbursement) outside the U.S. may also fall short a direct correlation to patient size. Accordingly, we see the Ex-U.S. opportunity for APL-130277 at around 1.5x the size of the U.S., or around $300 million. In total, we think APL-130277 is a $500 million opportunity for Cynapsus.

Product Revenue Model

Cynapsus Therapeutics	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
American's with Parkison's	0.950	0.964	0.979	0.993	1.008	1.023	1.039	1.054	1.070	1.086	1.103
Percent with "OFF" Issues	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*
Target PD Population	0.475	0.482	0.489	0.497	0.504	0.512	0.519	0.527	0.535	0.543	0.551
Percent "Mild"	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*
Mild Patients	0.166	0.169	0.171	0.174	0.176	0.179	0.182	0.185	0.187	0.190	0.193
Uses Per Day	1	1	1	1	1	1	1	1	1	1	1
Penetration Rate	*0%*	*0%*	*0%*	*0%*	*0.5%*	*1.0%*	*1.5%*	*2.0%*	*2.5%*	*2.5%*	*2.5%*
Total Daily Useage in MILD-PD	0.000	0.000	0.000	0.000	0.001	0.002	0.003	0.004	0.005	0.005	0.005
Percent "Moderate"	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*
Moderate Patients	0.238	0.241	0.245	0.248	0.252	0.256	0.260	0.264	0.268	0.272	0.276
Uses Per Day	2	2	2	2	2	2	2	2	2	2	2
Penetration Rate	*0%*	*0%*	*0%*	*0%*	*1.0%*	*2.0%*	*3.0%*	*4.0%*	*4.5%*	*5.0%*	*5.0%*
Total Daily Useage in MOD-PD	0.000	0.000	0.000	0.000	0.005	0.010	0.016	0.021	0.024	0.027	0.028
Percent "Severe"	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*
Severe Patients	0.071	0.072	0.073	0.075	0.076	0.077	0.078	0.079	0.080	0.081	0.083
Uses Per Day	3	3	3	3	3	3	3	3	3	3	3
Penetration Rate	*0%*	*0%*	*0%*	*0%*	*1.0%*	*2.5%*	*4.0%*	*5.0%*	*6.0%*	*6.5%*	*6.0%*
Total Daily Useage in SEV-PD	0.000	0.000	0.000	0.000	0.002	0.006	0.009	0.012	0.014	0.016	0.015
Total SL Units / Year	0.000	0.000	0.000	0.000	2.990	6.490	10.095	13.373	15.771	17.445	17.254
Price Per SL Unit	*$0*	*$0*	*$0*	*$0*	*$8.00*	*$8.64*	*$9.24*	*$9.80*	*$10.39*	*$11.01*	*$11.67*
U.S. Sales At Partner	**$0**	**$0**	**$0**	**$0**	**$23.9**	**$56.1**	**$93.3**	**$131.0**	**$163.8**	**$192.1**	**$201.4**
RoW Sales At Partner	**$0**	**$0**	**$0**	**$0**	**$17.9**	**$49.1**	**$93.3**	**$147.4**	**$204.8**	**$264.1**	**$302.1**

…Financials & Capital Needs…

Cynapsus exited the second quarter ended September 30, 2013 with $3.4 million in cash and investments. We note the company raised approximately $6.69 million net cash in the first quarter through the offering of common stock and warrants to purchase common stock. The company also converted $4.03 million in debt to equity during the first quarter 2013. As such, the balance sheet has improved dramatically. Below is a representation of the key balance sheet metrics as of year-end 2012, December 31, 2012 and as of the end of the September 30, 2013 quarter.

Balance Sheet	December 31, 2012	September 30, 2013
Cash and Cash Equivalents	$0.050 million	$3.409 million
Total Current Assets	$0.376 million	$3.544 million
TOTAL ASSETS	**$1.169 million**	**$4.301 million**
Total Current Liabilities	$6.179 million	$1.925 million
NET WORKING CAPITAL	($5.803 million)	$1.619 million
TOTAL LIABILITIES	**$6.179 million**	**$1.925 million**
SHAREHOLDER EQUITY	**($5.010 million)**	**$2.377 million**

Above shows the admirable job management has done over the past six months to raise cash and clean up the balance sheet. We note the company was listed on the OTXQX exchange July of this year. We see this move as a stepping-stone to a potential major exchange listing, such as the NASDAQ-CM in 2014 once the clinical development of APL-130277 has been pushed into the bioequivalence study.

The company's stated goal is to develop APL-130277 to the point where the U.S. new drug application (NDA) is ready for filing. We suspect that will take place during the second half of 2015. To get there, the company will need to complete the CTH-103 pilot study (majority funded back MJFF) and then conclude the bioequivalence study and follow-up safety work. Below we outline the proposed cost to develop APL-130277 to the company's stated goal.

CTH-201 Pivotal BEQ Study	$4.0 million
CTH 301 Safety Analysis	$8.5 million
Operating Overhead (April 2013 – December 2015)	$10.0 million
GROSS CAPITAL NEED	**$22.5 million**
Cash on hand as of September 30, 2013	$3.4 million
NET CAPTIAL NEED	**$19.0 million**

As of September 30, 2013, the fully-diluted share count stands at 62.029 million shares.

Basic Share Count	38.844 million
Stock Options	2.691 million
Warrants (5-year @ $0.575 / share)	13.062 million
Warrants (2-year @ $0.575 / share)	4.381 million
Warrants (other @ $0.575 / share)	3.431 million
Warrants (other @ $0.625 / share)	0.478 million
Warrants (other @ $1.00 / share)	0.127 million
Total Fully Diluted Shares	**63.127 million**

The U.S. OTC stock is trading at $0.371 per share. This equates to a market capitalization on a fully-diluted basis of $23.4 million. From an investment standpoint, with a market capitalization of only $22.5 million and the cost to develop to the new drug application of only around an additional $19 million, we see Cynapsus as having an excellent shot at creating significant shareholder value and providing substantial ROI to investors. Above we noted the peak sales estimate for APL-130277 at around $500 million worldwide ($200 million U.S. + $300 million Ex-U.S.). We believe the company may look to secure additional funding in 2014, after the move to the OTCQX and the data from the pilot study has presented.

Intellectual Property

Cynapsus has developed APL-130277 in a bilayer thin-film polymer matrix, with the active pharmaceutical ingredient (apomorphine) in one layer and an enhancer buffer in the other. Management tells us this improves bioavailability, reduces irritation, and increases stability. The thin-film is rapidly dissolving and allows for fast absorption of the API in doses ranging from 2 to 60 mg.

The company has undertaken a patent strategy that includes 3 patent applications and 1 granted patent:

- On June 12, 2010, the company filed its first utility application (12/813,82) claiming a variety of compositions and use of apomorphine products to treat Parkinson's disease. This first patent application is progressing normally through the USPTO and PCT National Phase examinations. This first patent seeks the broadest protections.

- In December 18, 2011 (13/445,656), the company filed a second patent application which protects more specific compositions and ingredients tested in preclinical models and man, and covers the anticipated commercial products. This second patent application is progressing normally through the USPTO and is ready to enter PCT National Phase examinations.

- On April 12, 2012, the company extracted a small set of claims from the 2nd family core patent and requested Track 1 examination at the USPTO. Track 1 is a fast-tracked review by the USPTO allowing expedited review of claims and a decision on patentability within a year. This allows the company to get provides valuable insight into potential objections by the patent office that can be useful during review of the company's other pending and future patent applications. In December 2012, the company announced a Notice of Allowance from the U.S. Patent and Trademark Office (USPTO) for claims covering (a) thin film compositions containing apomorphine formulated for sublingual administration (APL-130277) and (b) methods of use in Parkinson's disease. The application was granted US 8,414,192 (April 9, 2013).

- On April 8, 2013, a continuation application (13/858,638) was filed and Track 1 review was also requested. This application has a set of claims limited to 2 specific key elements of the composition that provide for the combined performance and stability of the formulation.

We see the key to the protection of APL-130277 as the formulation of the product and the PK curves that the clinical data will generate. These types of "pharmacokinetic patents" have been highly defensible in the past by companies such as Purdue Pharma, Depomed, and Transcept Pharma. For a company to develop a generic alternative to APL-130277 sublingual thin-film, they will have to do so without the patent-protected combination of formulation innovations Cynapsus has claims on, and demonstrate that their product achieves PK bioequivalence to Cynapsus' material or to the reference product in clinical testing similar to what the company is undertaking with APL-130277.

Management believes that “work-arounds” will be complex or unfeasible as they attempt to reproduce the intricate balance of parameters required to meet all the requirements of a commercial product (eg, processable, stable, easy handling, acceptable taste, etc…) with the performance needed for a fast-acting rescue therapy in Parkinson’s disease (eg, very fast dissolution, fast absorption, non-irritant, etc…). We remind investors that apomorphine formulation into an oral tablet is unlikely given that first-pass metabolism degrades the molecule into inactive metabolites.

The granted patent, US 8,414,192, is expected to protect the exclusivity of APL-130277 in the U.S. to 2031. Cynapsus has filed patent applications in all major markets in North America, Europe, Asia, and South America and continues to work with patent advisors (Clark & Elbing, Boston) and examiners in an attempt to strengthen the protection of product from potential generic competition beyond 2031.

MANAGEMENT BIO

Anthony Giovinazzo (President and CEO) has 35 years of experience in international investment and operating management, with an emphasis in strategy, mergers and acquisitions, financial management and business development. He has been involved in the neuroscience field since 1994. In this 19 year period he has obtained significant experience in the clinical development and commercialization of Alzheimer’s, Parkinson’s, Anxiety and Neuropathic Pain drug candidates. He is currently the President and CEO of Cynapsus. Most recently, he was the Founder, President and CEO of Cervelo Pharmaceuticals, a VC-backed company that raised US $36M in October 2007, CEO of Cita NeuroPharmaceuticals Ltd., which was later sold to a UK public company for an above market return to the investors, President of the Neuroscience Partners Fund and a Vice President and Partner at MDS Capital Corp. For 15 years, prior to joining MDS Capital Corp., he focused on international corporate tax, merchant banking and venture capital investing in Europe and the US. Mr. Giovinazzo is a Chartered Director and Audit Committee certified, and completed the Leadership and Strategy in Pharmaceuticals and Biotech Program of the Harvard Business School in June 2006. In 2010, he was reappointed to a 2nd 3-yr term as expert advisor to the NRC’s Phase 4-Genomics Funding Program.

Dr. Albert Agro (Acting CMO) will focus on the development of Cynapsus' Parkinson’s program and, subject to further financings in 2010, will join the company as Chief Medical Officer. Dr. Agro previously held a position as Sr. VP, Drug Development at TransTech Pharma (2007-2009), as Partner and VP Medical/Scientific Affairs at Axon (2003-2007), Director National Medicine and Director Immunology-Virology-Respiratory Medicine at Boehringer Ingelheim (2000-2003) and as Associate Director Cardiopulmonary Medicine at Bayer (1998-2000). Dr. Agro completed his Ph.D. from the Department of Medicine at McMaster University in 1995. After a post-doctoral fellowship at the University of Florence in Italy, Dr. Agro accepted an academic position as assistant professor in Pathology and Molecular Medicine at McMaster University in which he still maintains today. He is also the President and CEO of HNZ Strategic Holdings, Inc., a boutique consulting firm which provides clinical development services to pharma/biotech companies.

Dr. Nathan Bryson (CSO) draws from 20 yrs of experience in pharmaceutical development, having held scientific and executive management level positions at Flamel Technologies, Inc., Bionisis SA and Matregen Corp. Dr. Bryson has strong knowledge of early-stage drug product development and formulation and has co-authored more than 20 patents. He holds a BSc in Chemistry from Auburn University and a PhD in Chemistry from the Massachusetts Institute of Technology.

Andrew Williams (COO and CFO) is a co-founder of Cynapsus and has held senior management roles in other early stage businesses. Andrew has an economics degree from Queens University (1994) and an MBA from the Richard Ivey School of Business, University of Western Ontario (2001).

RECOMMENDATION: BUY

We maintain a buy rating and price target of $1.25 per share for Cynapsus. Despite limited volume and a market capitalization well below that of our typical coverage universe, we believe the company's focus on developing a sublingual form of the injectable Parkinson's drug apomorphine offers significant upside potential with a limited financial commitment, and that the company's commercial strategy to partner with a larger pharmaceutical organization presents meaningful upside to investors today.

Above we've outlined our belief that APL-130277 has peak U.S. sales of $200 million. Although this is somewhat lower than management's internal forecast of $284 million, we agree, in principal, with essentially all the company's conclusions about the opportunity. We see APL-130277 as a potential $500 million product worldwide.

Parkinson's disease (PD) is a progressive degenerative disease of the central nervous system that affects more than 1 million individuals in the U.S. and some 4 million in the developed world. The shortage of dopamine in the brain caused by the loss of dopaminergic neurons is believed to cause observable symptoms of paucity of movement and rigidity. Levodopa is the best known therapeutic agent for the treatment of PD. Unfortunately, while levodopa can result in improvement in symptoms of rigidity, patients can experience serious side effects including dyskinesia. This dyskinesia is often treated by lowering the dose of levodopa, which causes rigidity to return. This creates a situation where patients are fluctuating in clinical states between mobility and immobility for periods ranging from a few minutes to a few hours.

The fluctuations are manifested in various scenarios, including a "wearing-off' phenomena where deteriorations in the relief occurs before the next dose takes effect, but may be predictable given routine dosing schedules, or in an "on-off" phenomena where the transitions is more sudden and unpredictable. Clinical experience shows patients can switch from "on" to "off" and develop akinesia or rigidity in minutes or even seconds (Swope D M., 2004) with no discernible relation to a patient's dose schedule. Two other phenomena are the "delayed on", in which levodopa's effects are substantially delayed, and "no on" (dose failure), in which no effects occur at all.

Subcutaneous injections of apomorphine (Apokyn) have proved to be effective in the treatment of "on-off" fluctuations in PD within 5 to 15 minutes, and last for 45 to 90 minutes. Trials have shown consistent reversal of "off' period akinesia, a decrease in daily levodopa requirements and consequently a decrease in the amount of "on" period dyskinesias. Advantages of apomorphine include a quick onset of action, lower incidence of psychological complications, and a relatively short half-life. For these reasons, it is an ideal "rescue therapy".

Unfortunately, subcutaneous injections of apomorphine have proven to be impractical for patients entering a period of "wearing-off" or switching from "on-off" given most patients impaired motor function, diminished dexterity, and aversion to frequent painful injections. Furthermore, a common side effect of subcutaneous injection is the development of nodules, which often become infected, necessitating antibiotic treatment or surgical debridement (Prietz et al, 1998). Development of alternative formulations of apomorphine has been met with little success. For example, oral administration of apomorphine tablets has required high doses to achieve the necessary therapeutic effect because apomorphine administered by this route undergoes extensive first-pass metabolism. Intranasal administration produced transient nasal blockage, burning sensation and swollen nose and lips. Finally, sublingual administration of apomorphine tablets caused severe stomatitis on prolonged use with buccal mucosal ulceration in half the patients treated (Deffond et al, 1993).

We believe that the APL-130277 sublingual formulation of apomorphine offers an exceptional opportunity to address a well-established unmet medical need that is already a familiar pain point to practicing neurologists, the delivery of rescues therapy for OFF episodes without requiring movement-disordered patients to self-inject. The company seeks approval via a cost-effective bioequivalence pathway, and has already generated data that appears strongly predictive of a successful bioequivalence demonstration. Given the expected $500 million dollar worldwide market for such a product, and Cynapsus' current market capitalization of only $29.6 million, we believe that Cynapsus is an attractive investment for investors seeking to add a speculative and potentially high returning investment to their portifolio.

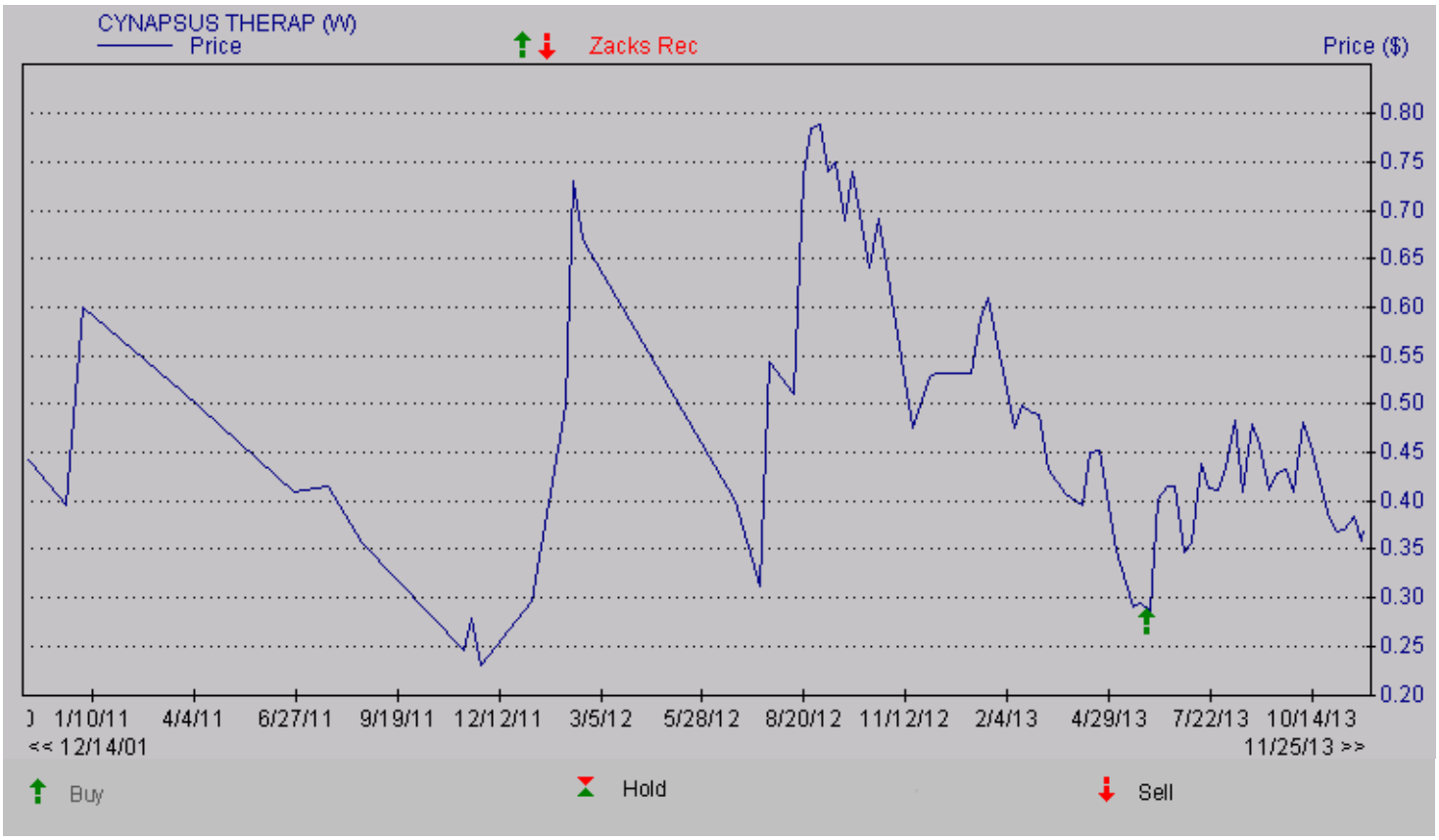
PROJECTED FINANCIALS

Cynapsus Therapeutics – Income Statement

Cynapsus Therapeutics, Inc.	2012 A	Q1 A	Q2 A	Q3 A	Q4 E	2013 E	2014 E	2015 E
APL-130277 WW Sales	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**
YOY Growth	-	-	-	-	-	-	-	-
Royalty Payments	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**
YOY Growth	-	-	-	-	-	-	-	-
Licensing & Collaborative	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$5.00**
YOY Growth	-	-	-	-	-	-	-	-
Total Revenues	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$5.00**
YOY Growth	-	-	-	-	-	-	-	-
Cost of Sales	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Product Gross Margin	-	-	-	-	-	-	-	-
Operating, General & Admin	$1.37	$0.39	$0.66	$0.74	$0.70	$2.49	$2.20	$3.00
Research & Development	$0.81	$0.14	$0.17	$0.40	$0.35	$1.07	$4.00	$5.00
Share-Based Comp	$0.34	$0.12	$0.22	$0.11	$0.10	$0.55	$0.50	$0.50
Amortization & Depreciation	$0.06	$0.02	$0.02	$0.02	$0.02	$0.06	$0.06	$0.06
Foreign Exchange	($0.01)	$0.01	$0.01	$0.01	$0.01	$0.04	$0.00	$0.00
Other Expenses	($0.09)	$0.76	($0.01)	($0.02)	$0.00	$0.73	$0.00	$0.00
Operating Income	($2.49)	($1.44)	($1.06)	($1.26)	($1.18)	($4.93)	($6.76)	($3.56)
Operating Margin	-	-	-	-	-	-	-	-
Grants & Other Income	$0.30	$0.12	$0.09	$0.00	$0.10	$0.31	$0.50	$0.25
Interest / Financing Net	($0.88)	($0.19)	($0.00)	($0.00)	($0.10)	($0.29)	($1.50)	($1.00)
Pre-Tax Income	($3.06)	($1.51)	($0.97)	($1.26)	($1.18)	($4.91)	($7.76)	($4.31)
Income Taxes Paid	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Tax Rate	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*
Net Income	($3.06)	($1.51)	($0.97)	($1.26)	($1.18)	($4.91)	($7.76)	($4.31)
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**($0.22)**	**($0.07)**	**($0.03)**	**($0.03)**	**($0.03)**	**($0.14)**	**($0.16)**	**($0.07)**
YOY Growth	*($0.20)*	-	-	-	-	*($0.37)*	*$0.09*	*($0.54)*
Basic Shares Outstanding	13.65	20.49	38.88	38.88	40.00	34.56	50.00	60.00

Source: Zacks Investment Research, Inc. *Jason Napodano, CFA*

HISTORICAL ZACKS RECOMMENDATIONS



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