Zacks Small-Cap Research

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# Cynapsus Therapeutics Inc. (V.CTH-TSX)

***CYNAF – Cynapsus Maps Out Clinical Plan For APL-130277…***

| | |
|---|---|
| **Current Recommendation** | **Buy** |
| Prior Recommendation | N/A |
| Date of Last Change | 07/23/2012 |
| Current Price (03/28/14) | $0.82 |
| **Target Price** | **$2.25** |

## UPDATE

Little known Toronto, Canada-based Cynapsus Therapeutics (CYNAF) is one of our best ideas for investment in the small-cap biotechnology sector. The company currently trades with a market capitalization of only $50 million, yet sits on a potential $750 million drug for the treatment of Parkinson's disease. The leading drug is APL-130277, a sublingual formulation of apomorphine, designed as a rescue medication for patients experiencing "off" time in-between their daily levodopa dosing. We like Cynapsus because the costs and risks to develop APL-130277 are low, and the exit strategy is clear – develop APL-130277 to the point where a new drug application (NDA) can be filed, and then sell the company to a larger pharmaceutical looking to commercial. Based on the data and market research that we have seen, Cynapsus shares offer a potential six-fold increase in returns.

## SUMMARY DATA

| | |
|---|---|
| **52-Week High** | **$1.26** |
| **52-Week Low** | **$0.29** |
| **One-Year Return (%)** | **N/A** |
| **Beta** | **N/A** |
| **Average Daily Volume (sh)** | **136,739** |
| **Shares Outstanding (mil)** | **40** |
| **Market Capitalization ($mil)** | **$33** |
| **Short Interest Ratio (days)** | **N/A** |
| **Institutional Ownership (%)** | **0** |
| **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 2014 Estimate** | **N/A** |
| **P/E using 2015 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) |
|---|---|---|---|---|---|
| 2013 | 0 A | 0 A | 0 A | 0 A | 0 A |
| 2014 | 0 E | 0 E | 0 E | 0 E | 0 E |
| 2015 | | | | | 0 E |
| 2016 | | | | | 0 E |

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

| | Q1 (Mar) | Q2 (Jun) | Q3 (Sep) | Q4 (Dec) | Year (Dec) |
|---|---|---|---|---|---|
| 2013 | -$0.07 A | -$0.03 A | -$0.03 A | -$0.02 A | -$0.13 A |
| 2014 | -$0.04 E | -$0.03 E | -$0.03 E | -$0.04 E | -$0.13 E |
| 2015 | | | | | -$0.13 E |
| 2016 | | | | | -$0.12 E |

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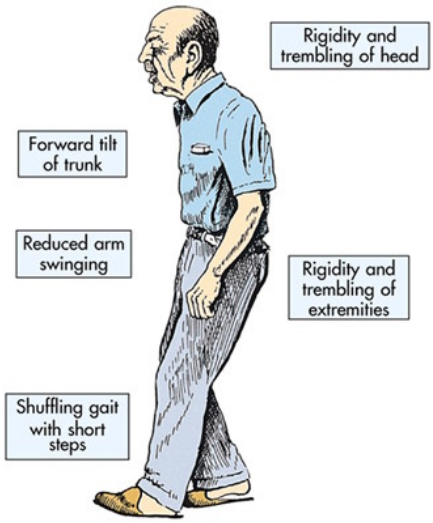
## WHAT'S NEW

Canada-based Cynapsus Therapeutics (CYNAF) remains one of our best ideas for investment in the small-cap biotechnology sector. The company currently trades with a market capitalization of only $52 million on a fully diluted share count, yet sits on a potential $750 million drug for the treatment of Parkinson's disease. The company's leading drug is APL-130277, a sublingual formulation of apomorphine, designed as a rescue medication for patients experiencing "off" time in-between their daily levodopa dosing. Apomorphine is a highly effective drug, already approved in the U.S. and around the rest of the world in various injectable formulations.

Our research into apomorphine leaves little doubt that the drug works. Sales, however, are greatly limited because Parkinson's patients experiencing "off" time struggle immensely with delivering a subcutaneous injection. A rapidly dissolving sublingual formulation of this highly effective drug will dominate the market. Cynapsus' market research shows significant interest from neurologists and movement disorder doctors, as well as the patients they treat. We like Cynapsus because the costs and risks to develop APL-130277 are low, and the exit strategy is clear – develop APL-130277 to the point where a new drug application (NDA) can be filed, and then sell the company to a larger pharmaceutical looking to commercial. Based on the data and market research that we have seen, Cynapsus shares offer a potential six-fold increase in returns.

**Quick Background On Parkinson's Disease**

Parkinson's disease (PD) is a slowly progressing neurological disorder characterized by tremor, stiffness and decreased movement, and postural instability affecting approximately 0.4% of the population over age 40 and 1% of those over age 65. The disease arises from the death of dopamine-generating cells in the substantia nigra region of the midbrain. The cause of PD is generally idiopathic, although some atypical cases have a genetic origin.

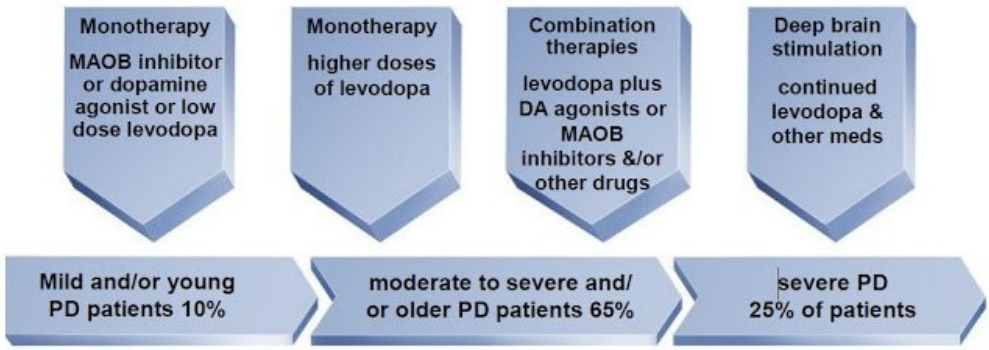



PD patients often exhibit marked reduction in motor control and an increase in parkinsonism (tremors, hypokinesia, rigidity, bradykinesia, and postural instability). Postural instability becomes more prominent as the disease progresses, resulting in difficulty walking and maintaining balance. Without 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.

As the disease progresses, patients often exhibit non-motor symptoms that include autonomic dysfunction, neuropsychiatric problems (mood, cognition, behavior or thought alterations, psychosis), and sensory and sleep difficulties. Parkinson's disease psychosis (PDP) is common in nearly 40% of PD patients a decade after initial diagnosis (Rabey, JM, 2009), and can often be induced by anti-Parkinson's drugs (Poewe W, 2003). Visual hallucinations are the most common clinical manifestation of the psychosis, along with dementia, anxiety, depression, and insomnia common co-morbidities.

**Treatment Options & The Problems That Exist For Patients**

There is no cure or disease modifying agent for PD. Instead, physicians attempt to manage the symptoms of the disease through a multidisciplinary approach that may include pharmacological, social, and surgical options. The most common pharmaceutical treatment options are those which look to increase the level of dopamine in the brain. These include dopamine replacement therapies (DRT) combined with dopa decarboxylase inhibitors, dopamine agonists, and MAO-B inhibitors. The treatment option is often tailored specifically for the patient based on the stage and severity of the disease and the balance between good symptom control and side-effects resulting from enhancement of dopaminergic function.




The most commonly used DRT therapy is Levodopa. It has been available in the U.S. for over 30 years. Levodopa (L-DOPA) is converted into dopamine in the dopaminergic neurons by dopa decarboxylase. The administration of Levodopa temporarily diminishes the motor symptoms associated with the lack dopamine in the substantia nigra. Carbidopa, a dopa decarboxylase inhibitor, is commonly dosed with Levodopa to prevent L-DOPA metabolism before it reaches the blood-brain barrier. In fact, co-formulations of Levodopa/Carbidopa (Sinemet-CR) are available.

Despite these co-formulations, Levodopa carries significant risk of side-effects, including dyskinesia (involuntary movements). As a result, despite its effectiveness in reducing motor symptoms associated with Parkinson's disease, physicians often attempt to delay Levodopa therapy until the disease progresses to a more moderate-to-severe stage. However, PD is a progressive and degenerative disease, and patients typically progress to the point where starting Levodopa or increasing the Levodopa dose is necessary in five years after initial diagnosis. After a decade on therapy, almost all PD patients require high doses of Levodopa, as well as surgical options including deep brain stimulation (DBS). As the dose and use of Levodopa increases, the incidence of Levodopa-induced dyskinesia (LID) also increases.

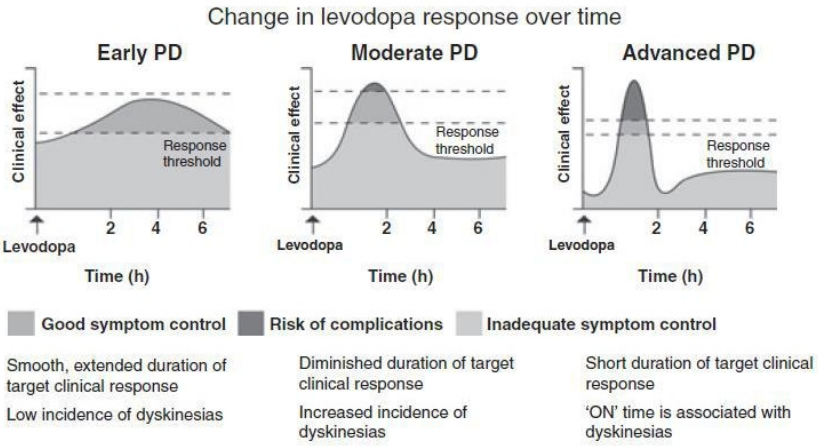
Levodopa also has a relatively short half-life, requiring dosing averaging three to four times a day. Peak plasma concentrations of Levodopa occur 60 to 90 minutes after dosing. The hefty dosing requirement of Levodopa creates compliance issues, especially at night when patients may sleep through their dose schedule – dosing every six hours. The peaks and troughs associated with Levodopa create significant "on" and "off" treatment times for PD patients. "On" times are when the drug is in their system and they may be experiencing dyskinesia, and "off" times are when the Levodopa has left their system and the patient may experience akinesia (a frozen or rigid state).

Early-morning akinesia is often the first motor complication of the PD patient. It primarily occurs after the patient awakes from a 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" because peak Levodopa plasma levels do not occur until 60+ minutes after dosing. Patients may misguidedly take a higher than prescribed initial morning dose of Levodopa, hoping to obtain a quicker on. Unfortunately, this can lead to severe dyskinesia.

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. It occurs in as many as 25% of patients within six months of the initiation of Levodopa therapy and as many as 50% within the first 18 months. The unpredictability of this sudden akinesia 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.

**Narrowing Of The Therapeutic Window**

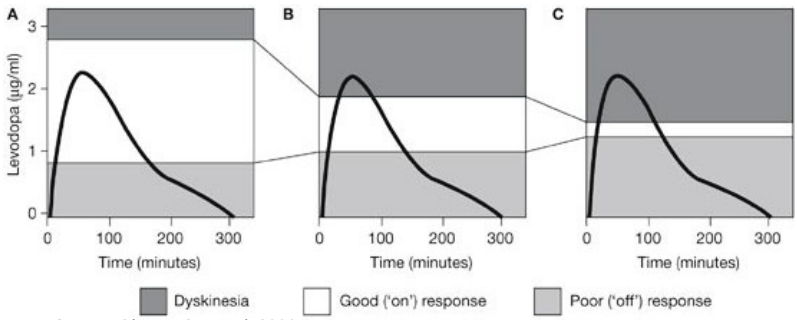
A paper by Schapira et al in the European Journal of Neurology entitled, "Levodopa in the treatment of Parkinson's disease" (2009,16:982-989), the authors note: "Early Parkinson's disease is associated with a prolonged response to Levodopa. Disease progression and Levodopa characteristics, e.g. short 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 below 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".




Source: Schapira et al, 2009

The picture above is representative of the narrowing of the therapeutic window and the diminishing respond to Levodopa therapy for advanced Parkinson's patients. The therapeutic window is the range of drug dosages that can treat disease effectively whilst staying within the safety range. In other words, it is the dosages of a medication between the amount that gives an effect (effective dose) and the amount that gives more adverse effects than desired effects. Therapeutic windows are dependent on the indication, often vary between individuals and can even evolve over time.

Below is schematic representation of the therapeutic window for aging response to Levodopa published by Olanow CW et al in Nature Clinical Practice – Neurology, in a paper entitled, "Continuous Dopaminergic Stimulation in the Treatment of Parkinson's Disease" (2006,2:382-392).

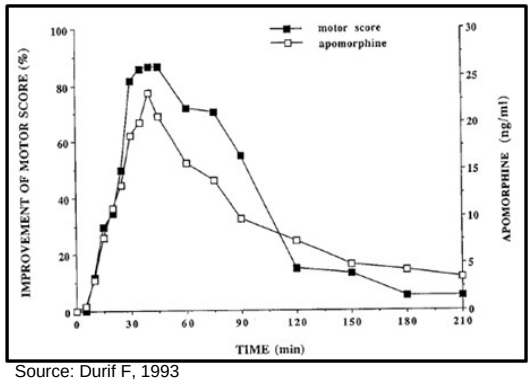



Source: Olanow CW et al, 2006

At the beginning of treatment (A), the therapeutic window is wide and patients exhibit good response to Levodopa therapy. As the window narrows (B), patients begin to exhibit dyskinesia at peak Levodopa plasma concentrations. Poor response, or "off time" increases as response to Levodopa wans. Patients may attempt to compensate for the waning Levodopa response and increased "off time" by increasing the Levodopa dose or frequency. This only leads to acceleration of the narrowing of the therapeutic window and increase Levodopa-induced dyskinesia. Patients with advanced Parkinson's disease (C) experience both severe dyskinesia following Levodopa dose and rapid return to "off time". Neurologists and movement disorder doctors note it becomes increasing difficult to deliver an effective dose of Levodopa to patients with advanced disease.

**Apomorphine To The Rescue – Sort Of**

Apomorphine hydrochloride injection (Apokyn®) is used as needed to treat "off" episode motor symptoms, such as muscle stiffness, slow movements, difficulty starting movements, and akinesia in people with advanced Parkinson's disease (PD). Apomorphine is a dopamine agonist that binds to the dopamine receptor to facilitate movement. Dopamine agonists are different from Levodopa in that they require minimal active neurons in the substantia nigra to be effective. Use of apomorphine as a rescue medication has been shown to be superior to rapid-acting, inhaled formulations of Levodopa for this exact reason. Clinical data generated by Durif F., et al published in Clinical Neuropharmacology (Vol.16;Issue2) in April 1993 confirms the strong PK-PD correlation between apomorphine plasma concentration in improvement in motor score (UPDRS).



Source: Durif F, 1993

In patients with advanced Parkinson's disease, 70-80% of the dopaminergic neurons in the substantia nigra have been lost, rendering drugs like Levodopa less effective over time (Khora SP et al, 2007). However, dopamine agonists, like apomorphine, act directly at the post-synaptic dopamine receptor, bypassing the need for dopamine. Because apomorphine is very fast acting (efficacy to "on" is as little as 5 minutes), it is ideally suited as rescue therapy allowing a patient that is "off" to regain mobility (Stacy M, et al, 2008).

Unfortunately, apomorphine (approved by the U.S. FDA as Apokyn® in 2004) is currently available only as a subcutaneous injection, which is completely impractical for a Parkinson's patient in the midst of an "off" episode to self-administer. Imagine a patient with advanced Parkinson's disease, lacking fine motor control, potentially experiencing dyskinesia, entering or already in a frozen state – and now take a look at the 27-page Instructions For Use for Apokyn®. We present some of the details below:



Source: U.S. WorldMeds, LLC 2014

These detailed and difficult to perform instructions render a highly effective drug nearly useless; and place significant logistical burden on the Parkinson's caregiver. They also place economic burden on the Parkinson's patient to pay for the caregiver or enter a long-term care facility.

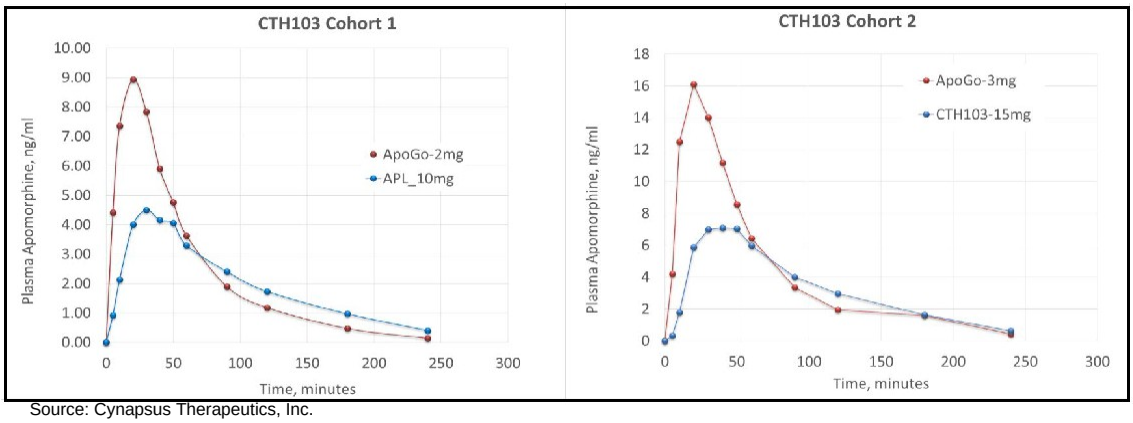
**Cynapsus' Better Solution: A Sublingual Formulation of Apomorphine**

Toronto-based Cynapsus Therapeutics (TSXV:CTH) is developing APL-130277, a fast-dissolving, fast-acting thin film formulation of apomorphine that is administered orally. 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 the sublingual formulation route include rapid uptake into the bloodstream and convenience. Above we noted the 27-page slide presentation on the instructions for use for Apokyn®. Patients do not like needles, and Parkinson's patients specifically have immense difficulty with a subcutaneous injection. The instructions for use on APL-130277 are simple and clear – open the packet and place one thin film on the tongue, then let dissolve. Data from the recently completed CTH-103 study demonstrates complete disintegration in roughly two minutes.

In January 2014, Cynapsus reported results from the aforementioned CTH-103 study. The CTH-103 study was a three-dose active comparator, placebo-controlled, randomized cross-over trial to examine the pharmacokinetic profile of sublingual administered APL-130277 compared to the subcutaneous injection of apomorphine in healthy volunteers. The goal of the study was to show that Cynapsus had formulated doses of APL-130277 that closely mimicked an injectable apomorphine comparator. For CTH-103, a trial conducted outside the U.S., Cynapsus used Apo-Go®, a similar product to the U.S. branded, Apokyn®. If Cynapsus could demonstrate blood plasma levels (AUC) that are in the range of 80% to 125% that produced by Apo-Go®, along with other things like the time to peak serum concentration, a confirmatory study with Apokyn® would be conducted in the U.S. and the new drug application (NDA) would be filed via the 505(b)(2) pathway claiming bioequivalence to the reference product.

The data, however, did not show bioequivalence ranging between 80% and 125%. For instance, APL-130277 achieved an apomorphine mean $T_{MAX}$ of 31 and 40 minutes for the 10 mg and 15 mg formulations, respectively. The subcutaneous injection (Apo-Go®) achieved apomorphine $T_{MAX}$ of 27 and 24 minutes for the 2 mg and 3 mg formulations, respectively. The mean time to reaching a plasma concentration of apomorphine associated with therapeutic benefit of "time to on" was 10-13 minutes for the two doses of APL-130277 versus 4-5 minutes for the subcutaneous injection. Below we present the pk curves for the two doses.



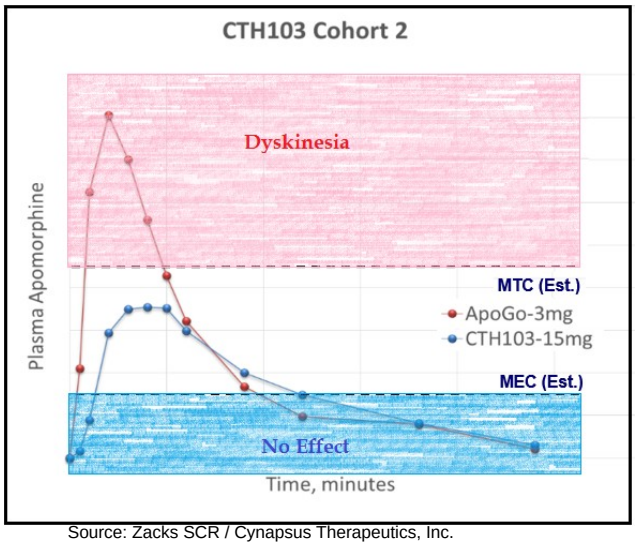
Source: Cynapsus Therapeutics, Inc.

On first glance, the graphs above seem to show that Cynapsus has some formulation work to do before they can progress down the bioequivalence path seeking U.S. FDA approval via the 505(b)(2) pathway. It looks like APL-130277 achieves far less peak plasma concentration than the injectable formulation. Although this statement is technically correct, assuming this means APL-130277 is inferior to the injectable Apo-Go® or Apokyn® is a broad misinterpretation of the clinical utility of the drug.

Interpreting the data from the CTH-103 study takes understanding of the therapeutic window discussed above. According to the U.S. FDA's Apokyn® summary basis for approval (SBA) and corroborating scientific literature we found separately, the minimum efficacious concentration (MEC) for Apokyn® is 3.5 ng/ml. We cite data by Durif F., et al published in Clinical Neuropharmacology (Vol.16;Issue2) in April 1993 concluding that "on" effect of apomorphine occurred at 3.2-3.6 ng/ml, where "on" was defined as a 25% improvement in UPDRS score.

This work was validated by studies conducted by VanLaar T., et al published in Clinical Neuropharmacology (Vol.21;Issue3) in May 1998 where the authors looked at stepwise increases of intravenous apomorphine and measured both MEC and the maximum tolerated concentration (MTC). VanLaar T, et al concluded that the MEC was around 3.9 ng/ml. Therefore, all plasma concentrations below the MEC do not reduce (or return the patient to) "off" time. VanLaar T, et al concluded that the MTC is 8.5 ng/ml. Therefore, all plasma concentrations above the MTC confer adverse side effects and tolerability issues, namely nausea, vomiting, and dyskinesia that make the drug undesirable to physicians and patients.

Inserting the MEC and MTC into the pk curve graphs above paints a dramatically different picture of APL-130277. Investors can see, not only does the 15 mg sublingual formulation of APL-130277 have a far rounder and smoother peak plasma concentration below the MTC, it also has a longer duration of action within the therapeutic window. APL-130277 never spiked blood plasma concentrations above the MTC (shaded in red), suggesting limited adverse events like nausea, vomiting, and dyskinesia. The duration of action above the MEC (shaded in blue) was also longer, at roughly 120 minutes vs. Apo-Go® 3 mg at roughly 85 minutes. Our conclusion is that APL-130277 offers superior pharmacokinetics to the injectable formulation.



Source: Zacks SCR / Cynapsus Therapeutics, Inc.

Safety and tolerability data from CTH-103 seems to back-up this claim. Below we present the adverse event profile for the first two cohorts of the CTH-103 study. We note that the original design of the CTH-103 study called for three cohorts, with a 25 mg APL-130277 dose to be compared to a 4 mg injectable dose. However, study investigators halted the study after the second cohort because patients had such severe and limiting side effects to the 3 mg injectable dose. One patient receiving 3 mg Apo-Go® even had a seizure. The 3 mg injectable formulation blew past MTC within minutes of administration. This resulted in roughly 2x the adverse event profile of Cynapsus' APL-130277 at 15 mg. Thus, the 25 mg APL-130277 strip was never tested in CTH-103.

| | S.C 2mg (n=15) | APL 10mg (n=15) | S.C 3mg (n=14) | APL 15mg (n=14) |
|---|---|---|---|---|
| # of subjects with AEs | 9 | 5 | 14 | 7 |
| # of subjects with Moderate AEs | 5 | 2 | 10 | 3 |

Source: Cynapsus Therapeutics, Inc.

On March 28, 2014, Cynapsus reported interim results from the CTH-104 study, a single dose, single arm, placebo-controlled, healthy volunteer pharmacokinetic study, designed to examine the pharmacokinetic profile of the 25 mg dose of APL-130277 without an active comparator. We note data released on March 28, 2014 is only an interim analysis of the first nine patients (7 on drug / 2 on placebo). CTH-104 enrolled a total of sixteen patients (14 on drug / 2 on placebo). Full data will be released in the next 15-30 days. However, the company felt as though this interim analysis was worth sharing with investors. Key findings from the initial look at CTH-104 were:

1) Comparing the increased dose of the 25 mg APL-130277 strip used in CTH-104 to that of the 15 mg strip previously used in CTH-103, the results indicates that a higher blood concentration of apomorphine was achieved. This is important because not only does is show potential for dose titration and proportion, but it puts to bed the question on the strips not being able to hold "enough drug" to achieve clinical efficacy.

2) In this first group of subjects, the pharmacokinetic profile of the 25 mg APL-130277 dose strip indicates that exposure increased as compared to 15 mg strip and achieved a concentration associated with an expected minimum efficacious concentration (MEC) of approximately 3 ng/ml for over 2 hours. This is very impressive duration of action. Results from the 15 mg strip show duration of MEC at around 90-100 minutes, so clearly the 25 mg strip offers superior efficacy.

3) The press release does note, however, that in this first group of subjects, sublingual delivery of the higher 25 mg strip dose resulted in more adverse events with a greater severity than seen with the 15 mg dose. At this time, we are unsure if these adverse events will limit utility, as the press release did not mention if blood concentrations exceed the maximum tolerated concentration (MTC), and if so, for how long. The press release does note that the side effects were mild to moderate and were not defined to be dose limiting.

Ideally, the full results from CTH-104 in a few weeks will include a nice graph similar to the ones posted above showing the PK curves of the 25 mg strip inside the therapeutic window. The conclusion from Cynapsus' CTH-103 study is that Apo-Go® (and the nearly identical Apokyn®) have rather poor exposure inside the therapeutic window. Besides the impracticality of the subcutaneous injection, poor coverage within the therapeutic window greatly limits sales of these two drugs. A product like APL-130277 with far more convenient and simple dosing, less adverse events, and far longer duration of action has enormous market share grabbing – and expanding – opportunity.

**What's Next For Cynapsus**

For development of APL-130277 in the U.S., Cynapsus management plans to follow the 505(b)(2) regulatory pathway. To accomplish this, the company must show that its sublingual thin film strip formulation of apomorphine is identical to the approved reference subcutaneous injection, Apokyn®. Cynapsus is pursuing a label that will claim intended use as an acute rescue therapy for Parkinson's patients experiencing acute, intermittent hypomobility (i.e. "off" episodes) associated with advanced Parkinson's disease. This is identical to the description of the use for Apokyn®. However, management will also seek language in the label noting improved safety, tolerability, convenience, and duration of action. These differentiating characteristics will help drive market share gains vs. the establish product, as well as provide intellectual property protection once commercialized. We note Cynapsus has already been granted patents (US#8414922) that protect APL-130277 to 2031, with additional applications pending.

From an efficacy standpoint, the 505(b)(2) pathway will require statistically sufficient clinical evidence that Parkinson's patients experience management of their "off" episodes with APL-130277. Therefore, Cynapsus will be required to conduct two pivotal efficacy programs with a primary end point assessing changes in the Unified Parkinson's Disease Rating Scale Part III (UPDRS III) movement score. In addition, the application must include statistically sufficient clinical evidence of safety, specifically with respect to the oral administering and evidence of low to no oral irritation as a result of multiple daily exposures to the drug for an extended period.

Below we have outlined the company's proposed clinical pathway based on annual regulatory filings. Management has guided to a face-to-face meeting with the FDA in the second quarter 2014 to confirm this pathway.

CTH-105 PS → CTH-105 will be a small pilot study in varied patients with Parkinson's disease who are naïve to the use of apomorphine and who experience at least one daily "off" episode with a total duration of "off" in any 24-hour period of at least 2 hours. This study is planned to examine the effect of APL-130277 on relieving "off" episodes over a single day with a dose-titration used to determine dose strengths necessary for future clinical development. The CTH-105 study is expected to begin in mid-2014 subsequent to the acceptance of an Investigational New Drug (IND) application by the FDA. CTH-105 is expected to be completed by the end of Q3-2014.

CTH-200 BS → CTH-200 is planned to be a single dose, crossover comparative bioavailability and pharmacokinetic study in healthy volunteers. This study is designed to provide the clinical "bridge" to the FDA's finding of safety and efficacy for the reference listed drug (Apokyn®). The CTH-200 Bridging Study is expected to begin in mid-2014 subsequent to completion of CTH-105. It is expected to be complete by end of Q3-2014 and is required under the FDA's 505(b)(2) regulations to demonstrate comparability to the reference listed drug.

CTH-300A → A double-blind, placebo-controlled, parallel-design study with Parkinson's patients who have at least one "off" episode every 24 hours, with total "off" time of at least 2 hours. The primary end point will be the changes in the UPDRS III score (a measure of movement ability). Secondary endpoints will include time to "on", total "on" time, quality of life measures, and safety. Our best guess – a total of 36 apomorphine-naïve patients will be enrolled at 2:1 randomization.

CTH-300B → A double blind, placebo-controlled, three-way crossover design study with Parkinson's patients who are presently controlled with the use of apomorphine. We expect each patient will receive one day treatment with APL-130277, Apokyn, or placebo, with a six day washout period between each dose. Similar to CTH-300A, the primary endpoint being UPDRS Motor Section III, and secondary endpoints will include time to "on", total "on" time, quality of life measures, and safety.

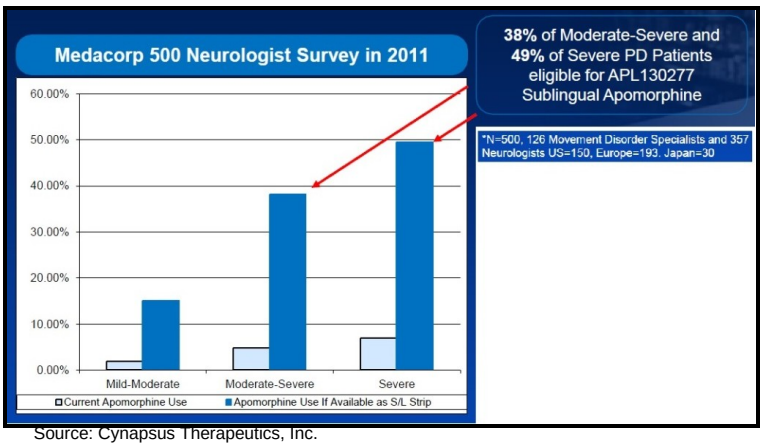
The company believes it can generate the data from CTH-300A and CTH-300B late 2014 / early 2015. If timelines hold, the second half of 2014 is going to be a pivotal inflection point for the valuation of Cynapsus shares. Upon successful completion of CTH-300a and CTH-300B, Cynapsus will provide the results to the FDA and request a meeting to seek final guidance for the design of Safety Study (CTH-301).

CTH-301 → This will be a long-term safety study in apomorphine naïve Parkinson's patients who have at least one "off" episode every 24 hours, with total "off" time of at least 2 hours. We suspect that approximately 100-150 apomorphine-naïve patients will be enrolled with a minimum exposure of 16 weeks. The primary endpoint for the study will be safety (oral irritation) with secondary endpoints examining efficacy as well as pharmacokinetic parameters. Management believes CTH-301 will begin early 2015 and be completed by the end of 2015.

Given the timelines noted above, we currently model the U.S. NDA filing around the middle of 2016. This would establish a PDUFA perhaps in the second quarter 2017.

## The Market Opportunity For APL-130277

Apokyn® and Apo-Go® are horribly impractical and inefficient drugs. Worldwide sales total only $70 million for injectable apomorphine, limited greatly by both poor physician and patient acceptance of the drug. We believe a far more convenient sublingual formulation that offers less side effects and longer duration of action will see dramatic increased use many multiples above the sales that injectable Apokyn® and Apo-Go® are doing now. Our belief is backed up by Medacorp survey of 500 Neurologist. Results of the survey (shown below) show a dramatic increase in use of the proposed profile for APL-130277 vs. the known profile for Apokyn®.




Source: Cynapsus Therapeutics, Inc.

We have looked in detail at the sales opportunity for APL-130277. According to the Parkinson's Disease Foundation, in the U.S. there are around one million Parkinson's patients. However, based on a growing elderly population, this number is expected to double by 2030. By 2024, the year in which we forecast peak sales for APL-130277, we project roughly 1.25 million Parkinson's patients in the U.S. Based on the above neurologist survey, 25-50% of PD patients experience "off" episodes. Our market research concludes that around 35% of patients are classified as mild, and might require one sublingual film per day. Another 50% of patients are classified as moderate, and might require two sublingual films per day. The remaining 15% are severe, and might require three or more sublingual films per day.

Based on the Medacorp survey above, current penetration rates for the injectable formulation are around 2%, 5%, and 7% for the mild, moderate, and severe populations. With APL-130277, penetration rates for all three classes of patient should dramatically increase. So not only will APL-130277 take dominate market share from the existing patients, it will bring in multiples of new patients not currently using apomorphine.

Apokyn® is currently being sold at around $3.25 per mg, with the 3 mg injection being the most common, resulting in a per injection price of around $9.75. We believe Cynapsus and its commercialization partner will be able to increase the price of APL-130277 modestly over the injectable formulation of apomorphine based on the improved convenience and potentially better clinical profile of lower side effects and longer duration of action. For the purpose of our model, we assume a conservative $10 per strip per day at peak. We assume the U.S. NDA will be filed in 2016, and the drug will be approved in 2017. We assume five years to peak market penetration (peak sales). Below is a breakdown of how we calculate peak sales of APL-130277.

***Peak Sales Estimate: APL-130277***

| ~1.25 Million U.S. Parkinson's Disease Patients by 2024 | Percent of PD Patients | Current Penetration Apokyn® | Estimated Penetration APL-130277 | Fold Increase | U.S. PD Patients On APL-130277 | Strips Needed Per Day | APL-130277 Strips |
|---|---|---|---|---|---|---|---|
| *- Estimated 35% with "OFF" Issues -* | | | | | | | |
| ***Mild Disease*** | 35% | 2.0% | 5.0% | 2.5 | 7,656 | 1 | 7,656 |
| ***Moderate Disease*** | 50% | 5.0% | 12.5% | 2.5 | 27,344 | 2 | 54,688 |
| ***Severe Disease*** | 15% | 7.0% | 17.5% | 2.5 | 11,484 | 3 | 34,453 |
| | | | | | | ***Total APL-130277 Strips Sold (at Peak)*** | 96,797 |
| | | | | | | ***Price Per Strip Per Day (at Peak)*** | $10 |
| | | | | | | ***Peak U.S. Sales (Millions)*** | $353 |

*Source: Zacks SCR / Jason Napodano, CFA*

The Parkinson's disease Foundation estimates the global prevalence of Parkinson's disease is around 4.5 million people. That includes the 1.0 million U.S. patients, so the Ex-U.S. market is around 3.5X the size of the U.S. market, at least in terms of patient population. Many of these patients are un-diagnosed, inaccessible, and live in countries that will never be targeted by the pharmaceutical company that promotes APL-130277. Others simply cannot afford the drug. For the purpose of our model, we assume the addressable Ex-U.S., primarily Europe and Japan, by 2022, will be around 2.0 million patients. Applying a modestly lower pricing and market breakdown analysis, we believe the Ex-U.S. revenue opportunity for APL-130277 is around $400 million.

**Conclusion & Valuation**

Our work leads us to believe the global market opportunity for APL-130277 at around $750 million. We bullet-point some of the key findings from our research:

→ Treatment of Parkinson's disease represents a large and substantially unserved market. There are an estimated 1 million U.S. PD patients, 25-50% with significant "off" issues.
→ Dosing dynamics for drugs like Levodopa and apomorphine are what drive sales – too much drug leads to dyskinesia and too little drug leads to increase "off" time (bradykinesia / akinesia).
→ The range between the maximum tolerated concentration (MTC) and minimum effective concentration (MEC) defines the therapeutic window.
→ The therapeutic window for Parkinson's disease rapidly closes as patient gain experience with Levodopa.
→ Apomorphine is a highly effective approved rescue medication for Levodopa "off" time.
→ Subcutaneous injectable apomorphine, sold in the U.S. as Apokyn®, is a horrible impractical and inefficient drug, flawed by its delivery system and quick peak-to-trough pharmacokinetic profile.
→ Sales of Apokyn® are limited by poor patient and physician acceptance.
→ Developing a sublingual formulation of apomorphine has a high chance of success given the excellent coverage of the therapeutic window seen in the CTH-103 and CTH-104 trial results.
→ Data from the CTH-103 study suggests that APL-130277 may offer a dramatically lower side effect profile and longer duration of action when compared to Apokyn®.
→ Data from the CTH-104 study suggest that 25 mg APL-130277 can provide apomorphine plasma concentrations above the MEC for roughly 2 hours, an estimated doubling of the therapeutic effect.
→ Data from the CTH-103 and CTH-104 study suggest safety and tolerability consistent with limited exposure above the MTC.
→ This improved profile should lead to a dramatic increase in market penetration. Company sponsored neurologist surgery (n=500) suggests 7.5-fold increase in penetration.
→ For the purpose of our financial model, we assume only a 2.5-fold increase in penetration.
→ Priced at only a modest premium to the injectable formulation, APL-130277 is a $350 million U.S. revenue opportunity at peak.
→ Global peak sales could hit $750 million.

Cynapsus has defined a clear exit strategy for shareholders. Develop the drug to the completion of the NDA and then sell the company. All-in costs to develop APL-130277 to this stage are estimated at around $25 million. Cynapsus has a current market capitalization of only $50 million on a fully-diluted basis. Fully-diluted share count would include cash in-flow of approximately $11.8 million from exercised warrants and $1.3 million in stock options. We expect the company will enter into a financing in the next few months to raise approximately half these funds. Fully financing APL-130277 to commercialization has been incorporated in our financial model, so price targets posted below include expected dilution from new shares.

We have conducted two separate valuation methods to value shares of Cynapsus Therapeutics. Applying a modest 3.5x sales multiple on our peak 2024 revenue assumption, and discounting back to present day at 25% with 50% probability of success, we calculate a potential take-out price of $276 million. We have also incorporated these forecasts into a 10-year DCF model with first sales posted in 2017, peak sales in 2024, 2% terminal growth rate, 10% cost of goods sold, 10% marketing costs, 35% effective tax rate after approximately $16.6 million in NOL's, and a similar 25% discount rate and 50% probability of approval. Our DCF analysis yields a fair-value of $224 million. Based on 63.1 million shares (current fully-diluted) with an estimated 20 million new shares required for future financings, we believe Cynapsus shares are fairly-valued today (average of our two methods) at $2.25 per share.

## PROJECTED FINANCIALS

### Cynapsus Therapeutics – Income Statement

| Cynapsus Therapeutics, Inc. | 2012 A | 2013 A | Q1 E | Q2 E | Q3 E | Q4 E | 2014 E | 2015 E | 2016 E |
|---|---|---|---|---|---|---|---|---|---|
| APL-130277 WW Sales | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0 |
| *YOY Growth* | - | - | - | - | - | - | - | - | - |
| Royalty Payments | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0 |
| *YOY Growth* | - | - | - | - | - | - | - | - | - |
| Licensing & Collaborative | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0 |
| *YOY Growth* | - | - | - | - | - | - | - | - | - |
| **Total Revenues** | **$0** | **$0** | **$0** | **$0** | **$0** | **$0** | **$0** | **$0** | **$0** |
| *YOY Growth* | - | - | - | - | - | - | - | - | - |
| Cost of Sales | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0 |
| *Product Gross Margin* | - | - | - | - | - | - | - | - | - |
| Operating, General & Admin | $1.37 | $2.64 | $0.80 | $0.85 | $0.90 | $0.90 | $3.45 | $3.00 | $3.00 |
| Research & Development | $0.81 | $1.63 | $0.85 | $0.75 | $1.00 | $1.25 | $3.85 | $5.00 | $5.00 |
| Share-Based Comp | $0.34 | $0.52 | $0.15 | $0.20 | $0.10 | $0.10 | $0.55 | $0.55 | $0.55 |
| Amortization & Depreciation | $0.06 | $0.06 | $0.02 | $0.02 | $0.02 | $0.02 | $0.06 | $0.07 | $0.07 |
| Foreign Exchange | ($0.01) | $0.04 | $0.01 | $0.01 | $0.01 | $0.01 | $0.04 | $0.00 | $0.00 |
| Other Expenses | ($0.09) | ($0.04) | ($0.05) | ($0.05) | ($0.05) | ($0.05) | ($0.20) | ($0.02) | ($0.02) |
| Operating Income | ($2.49) | ($4.85) | ($1.78) | ($1.78) | ($1.98) | ($2.23) | ($7.75) | ($8.60) | ($8.60) |
| *Operating Margin* | - | - | - | - | - | - | - | - | - |
| Grants & Other Income | $0.30 | $0.43 | $0.15 | $0.15 | $0.15 | $0.15 | $0.60 | $0.75 | $0.75 |
| Interest / Financing Net | ($0.88) | $0.01 | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 |
| Pre-Tax Income | ($3.06) | ($4.43) | ($1.63) | ($1.63) | ($1.83) | ($2.08) | ($7.15) | ($7.85) | ($7.85) |
| Income Taxes Paid | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 | $0.00 |
| *Tax Rate* | *0%* | *0%* | *0%* | *0%* | *0%* | *0%* | *0%* | *0%* | *0%* |
| Net Income | ($3.06) | ($4.43) | ($1.63) | ($1.63) | ($1.83) | ($2.08) | ($7.15) | ($7.85) | ($7.85) |
| *Net Margin* | - | - | - | - | - | - | - | - | - |
| **Reported EPS** | **($0.22)** | **($0.13)** | **($0.04)** | **($0.03)** | **($0.03)** | **($0.04)** | **($0.13)** | **($0.13)** | **($0.12)** |
| *YOY Growth* | *($0.20)* | *($0.43)* | - | - | - | - | *$0.06* | *($0.03)* | *($0.08)* |
| Basic Shares Outstanding | 13.65 | 34.67 | 41.00 | 56.00 | 57.00 | 58.00 | 53.00 | 60.00 | 65.00 |

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

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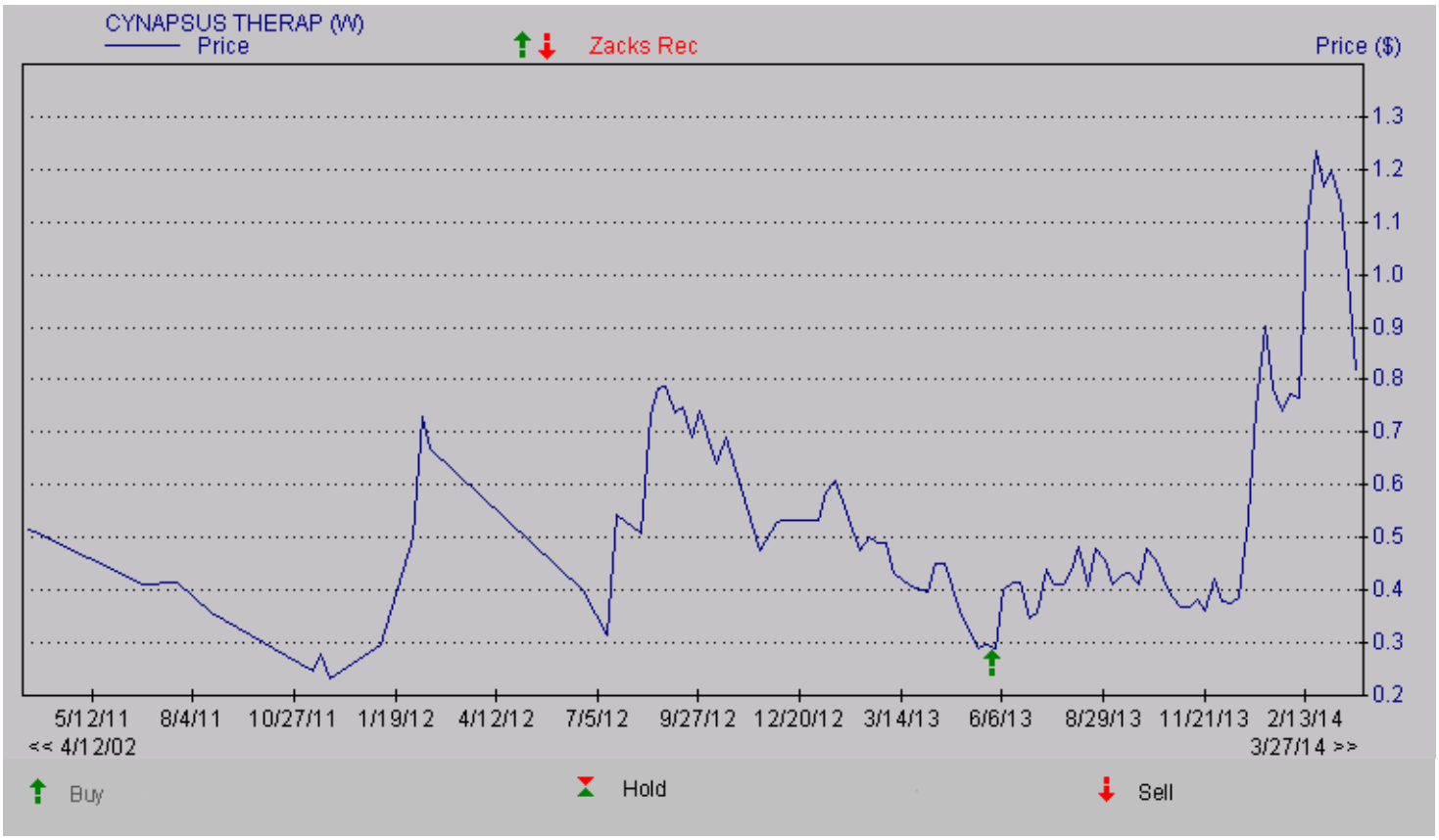

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