Zacks Small-Cap Research

March 10, 2016
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Cynapsus Therapeutics Inc.

(CYNA - NASDAQ)

CYNA: Annual Report 2015

Current Recommendation	**Buy**
Prior Recommendation	N/A
Date of Last Change	2/29/2016
Current Price (3/10/16)	$13.27
Target Price	**$30.00**

UPDATE

Cynapsus Therapeutics Inc. (CYNA) exited 2015 with a solid cash balance of roughly CDN$105 million (cash and cash equivalents).

The company hopes to continue enrollment for Phase 3 clinical trials for APL-130277, and anticipates submitting an NDA to the FDA by end of 2016/beginning 2017. The company is also making pre-approval commercialization efforts in the U.S. market, and initial regulatory and clinical activities for European market registration.

SUMMARY DATA

52-Week High	**$18.08**
52-Week Low	**$12.91**
One-Year Return (%)	**-11.43**
Beta	**1.22**
Average Daily Volume (sh)	**55,355**
Shares Outstanding (mil)	**12.2**
Market Capitalization ($mil)	**167**
Short Interest Ratio (days)	**12.04**
Institutional Ownership (%)	**47**
Insider Ownership (%)	**16.5**
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 2015 Estimate	**N/A**
P/E using 2016 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)
2014	0 A	0 A	0 A	0 A	0 A
2015	0 A	0 A	0 A	0 A	0 A
2016	0 E	0 E	0 E	0 E	0 E
2017					0 E

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

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2014	-$0.49 A	-$0.62 A	-$0.34 A	-$1.02 A	-$2.56 A
2015	-$0.97 A	-$1.50 A	-$0.24 A	-$0.70 A	-$2.98 A
2016	-$1.07 E	-$0.96 E	-$1.01 E	-$1.09 E	-$4.13 E
2017					-$4.16 E

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WHAT'S NEW

CYNA: Annual Report 2015

Financial Update

R&D expenses amounted to $27.4 million, which was close to our estimate ($26 million). This higher expenditure is related to the development of APL-130277, including the Phase 3 clinical program, patent protection, scale-up CMC work, share-based compensation, consulting fees, as well as costs associated with the increase in staff (from 17 to 25 people).

Operations, general and administrative expenses (OG&A) were $11.4 million. OG&A expense, was high, particularly in Q4 2015 ($3.7 million) as compared to the expense incurred in the first three quarters of 2015 (Q1=$1.78M, Q2=$2.04M, Q3=$1.82M). The increase was related to increases in investor and public relations activities, travel costs, professional and consulting fees, commercialization activities, salaries and benefits for the newly hired staff as well as higher employee base salaries.

The company reported a net loss of $27.5 million (-$2.97 EPS) for the year 2015. Loss adjusted for ForEx gains (significant strengthening of the U.S. dollar) amounted to roughly $40 million (-$4.35 EPS).

Cash used to run the company's operations during 2015 was roughly $32 million. As of December 31, 2015 the company sported a strong balance sheet with approximately $105 million in cash. We think the company will continue to incur relatively elevated expenses for R&D related to the completion of Phase 3 clinical trial, submitting an NDA with the FDA, clinical trials in Europe, as well as commercialization activities to prepare for the U.S. launch of APL-130277. We expect that as the company expands and adds personnel and infrastructure, they may have higher general and administrative expenses also. We think the cash on hand is sufficient to accomplish their goals for the 2016-2017 time frame.

Business Update

In order to continue development of APL-130277 in the U.S. under the section 505(b)(2) of the FDCA, Cynapsus plans on conducting the following clinical trials:

CTH-300 Phase 3 Efficacy Study: This double-blind, placebo-controlled, parallel-design trial across 35 sites was commenced during Q2 2015 (June 2015) to evaluate the efficacy and safety of APL-130277 versus placebo in an estimated 126 PD patient population. Subjects who have at least one OFF episode every 24 hours and a total OFF time of at least two hours per day will be enrolled into the study. Patients will be dosed at home as well as in the clinic, observed for 12 weeks and evaluated every four weeks. The primary end point is the mean change in the Unified Parkinson's Disease Rating Scale Part III (UPDRS Part III) score at 30 minutes after dosing and will be measured at week 12. The trial is expected to be completed in April 2016 and the company anticipates releasing top-line data by end Q2/beginning Q3 2016.

CTH-301 Phase 3 Safety Study: In Q3 2015 (September 2015) an open-label, Phase 3 study was commenced to examine the long-term safety, tolerability and efficacy of APL-130277 in PD patients who have at least one OFF episode every 24 hours, with total OFF time of at least two hours per day. A total of 226 patients are expected to be enrolled; 126 patients enrolled in the CTH-300 study plus an additional 100 new patients. The estimated completion time of this study is around mid-Q4 2016 and CYNA anticipates releasing top-line data by end Q4 2016/Q1 2017.

CTH-201 Phase 2 Thorough QT Study: A Phase 2, randomized, double-blind, placebo-controlled three-period crossover, positive control, QT-evaluation study employing APL-130277 may begin in 2H 2016 depending on FDA review and approval. The primary goal of this trial is to evaluate the effect of higher doses of APL-130277 compared to placebo on ECG parameters in patients who have at least one OFF episode every 24 hours, with total OFF time of at least two hours per day. The secondary goal of this trial is to evaluate the safety and pharmacokinetics of APL-130277 and the comparison of efficacy of the highest and lowest tolerated dose levels of APL-130277 that results in a full ON episode. If the trial is initiated as per plan then it is expected to be completed in Q4 2016/Q1 2017.

Once the clinical trials are completed CYNA believes it is on track to prepare and file the section 505(b)(2) NDA to the FDA by end 2016/beginning 2017 time frame. Further, the company plans on consulting with the European Medicines Agency (EMA) during the latter half of 1H 2016 to apply for regulatory approval in Europe. With regard to this an active comparator study in PD patients suffering from debilitating effects of OFF episodes (CTH-302: European Registration Study) is expected to commence in 2H 2016.

INVESTMENT THESIS

Cynapsus Raises Cash, Lists On NASDAQ

We remind investors that during the first quarter 2015, the company raised approximately $19.6 million in cash, with $3.5 million coming from shareholders exercising outstanding warrants and $16.1 million through a private placement of 1.375 million shares at $12.40 per share. The financing in late March 2015 was led by funds associated with OrbiMed, Aisling Capital and Venrock, with participation from various other institutional investors, including existing shareholders Broadfin Capital, Sphera Funds Management, Pura Vida Investments, DAFNA Capital Management and Dexcel Pharma Technologies Ltd / Dexxon Holdings Ltd. During the second quarter of 2015, the company completed an underwritten public offering in the U.S. of 5,175,000 common shares for net proceeds of $81.3 million (approximately US$66.4 million). The company also received $540k in proceeds from the exercise of warrants.

Cynapsus' cash balance is $82 million in September 2015. Management plans to use the cash as follows:

- → $30 million to fund the Phase 3 program (CTH-300, CTH-301, CTH-200)
- → $25 million to fund pre-approval commercialization efforts in the U.S.
- → $12 million to initiate clinical and regulatory activities in the EU
- → $5 million to complete CMC related expenses
- → $3 million to fund early-stage pipeline development

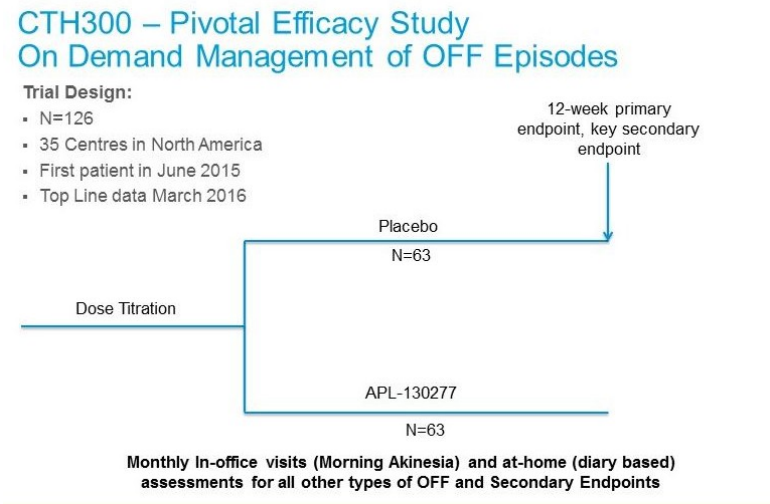
The basic share count is at roughly 12.1 million. The fully-diluted share count, which includes approximately 3.3 million warrants will be approximately 15.4 million. The basic market capitalization of the NASDAQ-listed shares is approximately $183 million ($233 million fully-diluted). Our financial modeling shows the shares are worth approximately $395 million on an enterprise value today. On a total value, probability-adjusted basis, we believe the NASDAQ-listed shares are worth $30.

Phase 3 Trial Underway!

The CTH-105 Phase 2 clinical trial was the first to test Cynapsus APL-130277. In February 2015, Cynapsus held a face-to-face meeting with the U.S. FDA to discuss the "end of Phase 2" and map-out the path forward toward the New Drug Application (NDA). In March 2015, the company provided to investors a road-map toward the U.S. NDA filing, which will be through the expedited 505(b)(2) pathway. To be in position to file for approval, the company must conduct two pivotal Phase 3 registration trials, an efficacy trial dubbed CTH-300 and an open-label safety trial dubbed CTH-301. The company must also conduct a bioavailability / bridging study comparing its drug to the Reference Listed Drug in Apokyn® (subcutaneous apomorphine injection), dubbed CTH-200.

- ✓ **CTH-300:** This is a double-blind, placebo-controlled, parallel-design study seeking to enroll an estimated 126 Parkinson's disease patients in 35 centers who have at least one OFF episode every 24 hours, with total OFF time of at least two hours per day (NCT02469090). The objective is to evaluate the efficacy and safety of APL-130277 versus placebo in patients with PD over a 12 week period. The primary end point will be the mean change in the Unified Parkinson's Disease Rating Scale Part III (UPDRS III) score at 30 minutes after dosing. The trial is expected to be completed in April 2016 and the company anticipates releasing top-line data by end Q2/beginning Q3 2016. Since APL-130277 is being compared to placebo, we view this trial as having a very high probability of success.

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- ✓ **CTH-301:** Cynapsus will also enroll a pivotal six month safety study that will consist of the 126 patients from the CTH-300 trial plus another 100 de novo patients. The primary endpoint of this study is safety, with analysis looking at adverse events, oral tolerability, and impact on cardiac function assessed by electrocardiogram. Enrollment in this trial commenced in September 2015, roughly 12 weeks after the first patient complete the placebo-controlled portion of CTH-300 study. The estimated completion time of this study is around mid-Q4 2016 and CYNA anticipates releasing top-line data by end Q4 2016/Q1 2017.



- ✓ **CTH-200:** The final step before the NDA filing is a short bridging study, planned to be a single-dose, crossover comparative bioavailability and pharmacokinetic (PK) study in healthy volunteers. This study is designed to allow Cynapsus to use the safety and efficacy data for the Reference Listed Drug (Apokyn®) in its 505(b)(2) NDA submission to the FDA. Management completed this study in December 2015.

- ✓ ***CTH-201:*** A Phase 2, randomized, double-blind, placebo-controlled three-period crossover, positive control, QT-evaluation study employing APL-130277 may begin in 2H 2016 depending on FDA review and approval. The primary goal of this trial is to evaluate the effect of higher doses of APL-130277 compared to placebo on ECG parameters in patients who have at least one OFF episode every 24 hours, with total OFF time of at least two hours per day. The secondary goal of this trial is to evaluate the safety and pharmacokinetics of APL-130277 and the comparison of efficacy of the highest and lowest tolerated dose levels of APL-130277 that results in a full ON episode. If the trial is initiated as per plan then it is expected to be completed in Q4 2016/Q1 2017.

Once the clinical trials are completed CYNA believes it is on track to prepare and file the section 505(b)(2) NDA to the FDA by end 2016/beginning 2017 time frame. Further, the company plans on consulting with the European Medicines Agency (EMA) during the latter half of 1H 2016 to apply for regulatory approval in Europe. With regard to this an active comparator study in PD patients suffering from debilitating effects of OFF episodes (CTH-302: European Registration Study) is expected to commence in 2H 2016.

In parallel to these studies, Cynapsus will be performing the necessary scale-up, process validation and stability as part of the Chemistry, Manufacturing and Controls (CMC) requirements for the filing of the NDA. In mid-March 2015, the company announced that it had entered into an agreement with ARx, LLC whereby ARx agreed to provide

Cynapsus with formulation, CMC and clinical unit production of APL-130277 and certain related services to support the planned clinical studies noted above. Under the terms of the agreement, ARx also assigned all of its right to the sublingual film patent family to Cynapsus. In return, Cynapsus granted ARx a non-exclusive license to this patent family in all fields other than generic APL-130277 applications. We remind investors that management has earmarked $5 million in funds to complete all the necessary CMC work prior to the NDA filing. Cynapsus has also earmarked $3 million for early-stage pipeline development, which we suspect includes exploring the use of additional drug candidates on the sublingual film technology.

If all the above goes smoothly, we believe Cynapsus will be in position to file the U.S. NDA application by end 2016/beginning 2017 time frame. With standard review, APL-130277 should receive a PDUFA date in the U.S. during the second half of 2017. We believe a take-out of the company is likely after the U.S. NDA filing.

Acorda Acquires Civitas And Validates The Market

We have been saying that the market opportunity for an effective rescue medication to treat off episodes in Parkinson's patients in a potential multi-hundred million-dollar opportunity. We estimated the peak U.S. sales for APL-130277 are around $700 million. We note that this does not include forecasts for sales in Europe or Asia, and as part of the planned activity over the next 12-18 months Cynapsus does intend to engage with European regulators to discuss the clinical and regulatory strategy for APL-130277 in the EU. As noted above, the company has earmarked $12 million in funds for this endeavor.

The prevalence of off episodes is significant in our view. According to various peer-reviewed literature (Muenter AJE, 2001; Rascol et al, 2000, Lopez I et al, 2010), after five years of treatment with levodopa, approximately 30-60% of all Parkinson's patients will experience wearing off episodes. After ten years of treatment with levodopa, virtually all PD patients (~95%) suffer from off episodes. We estimate there will be approximately 1.25 million PD patients in the U.S. by 2024 (year of peak sales). Our U.S. sales model for APL-130277 is show below.

~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	1.0	7,656
Moderate Disease	50%	5.0%	15.0%	3.0	32,813	2.5	82,031
Severe Disease	15%	7.0%	25.0%	3.6	16,406	4.0	65,625
						Total APL-130277 Strips Sold (at Peak)	155,313
						Price Per Strip (at Peak)	$12
						Peak U.S. Sales (Millions)	**$680**

Source: Zacks SCR / Jason Napodano, CFA

On September 24, 2014, Acorda Therapeutics announced it had made an offer to acquire privately-held Civitas Therapeutics for $525 million in cash. The impetus of the acquisition by Acorda was to get CVT-301, a Phase 3 inhaled formulation of levodopa for the treatment of off episodes in Parkinson's patients. With CVT-301, Acorda believes it has an attractive late-stage asset to add to the company's CNS-focused pipeline. The CVT-301 Phase 3 study began enrollment in December 2014. The estimated completion of the study with data is June 2016, putting Cynapsus drug about two months ahead. Nevertheless, the new drug application (NDA) for CVT-301 is also planned for late 2016, similar to APL-130277. Acorda estimates the market opportunity for CVT-301 is in excess of $500 million, consistent with what we believe and model. Civitas had been previously planning an initial public offering, but the $525 million all-cash offer from Acorda was simply too attractive to pass up.

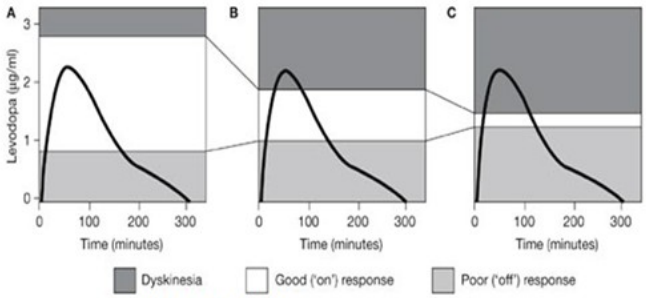
Specifically, CVT-301 is an inhaled formulation of levodopa. Levodopa is the most common form of dopamine replacement therapy, a backbone regimen and standard of care for the treatment of Parkinson's disease. Parkinson's disease is a slowly progressing neurological disorder characterized by tremor, stiffness and decreased movement. The decreased movement is a direct result of the lack of dopamine in the brain. Levodopa, when taken orally, is converted into dopamine in the substantia nigra 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

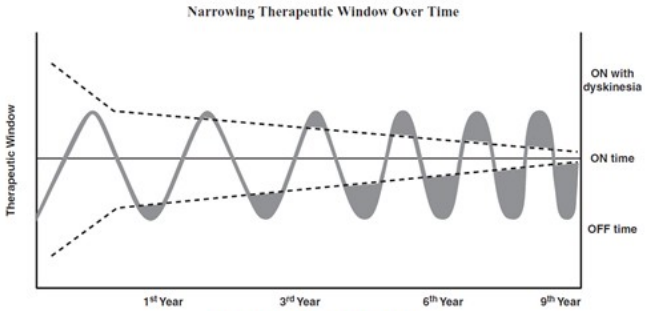
(Sinemet-CR) are available. Civitas' formulation of levodopa bypasses the gut metabolism through inhalation, a pathway known to for rapid uptake and onset of action.

There are, however, major limitations to the use of levodopa as a treatment for Parkinson's disease. Mainly, the patient must have substantial remaining dopaminergic neurons in the substantia nigra to metabolize the drug. However, according to research published in the Journal of Neural Transmission by P. Riederer et al in 1976, pathological studies of Parkinson's disease show at least 70-80% of the dopaminergic neurons are lost before the onset of symptoms. The effectively creates a "shelf-life" for levodopa treatment as the standard of care in patients with PD. This work was confirmed by K. Yoshikawa et al, 2004.

This explains why levodopa is very effective for a period of time, then wanes with disease progression. A newly diagnosed Parkinson's patient has the capacity, albeit diminished, to process levodopa. As the patient loses this capacity, the therapeutic window for levodopa therapy begins to narrow. Levodopa also has a relatively short half-life of only 60-90 minutes. The drugs effect, even in the mild Parkinson's patient, only lasts for 1.5 to 2.0 hours post dose (Brooks, D, 2008). Work done by Olanow et al, 2006 shows the therapeutic window for a Parkinson's disease patient rapidly closes (narrows) as patients gain experience with Levodopa use. This is due to a combination of disease progression, loss of dopaminergic neurons in the substantial nigra, and the short half-life of the drug (left). A similar graphical representation of this effect can be found in Cynapsus public filings (right).

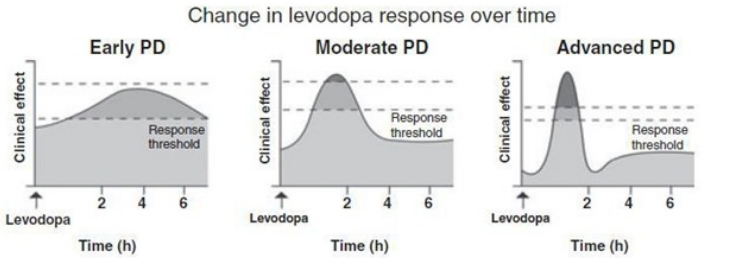


Source: Olanow CW et al, 2006
A: Naïve patient, B: Experienced patients, C: Severe PD patient



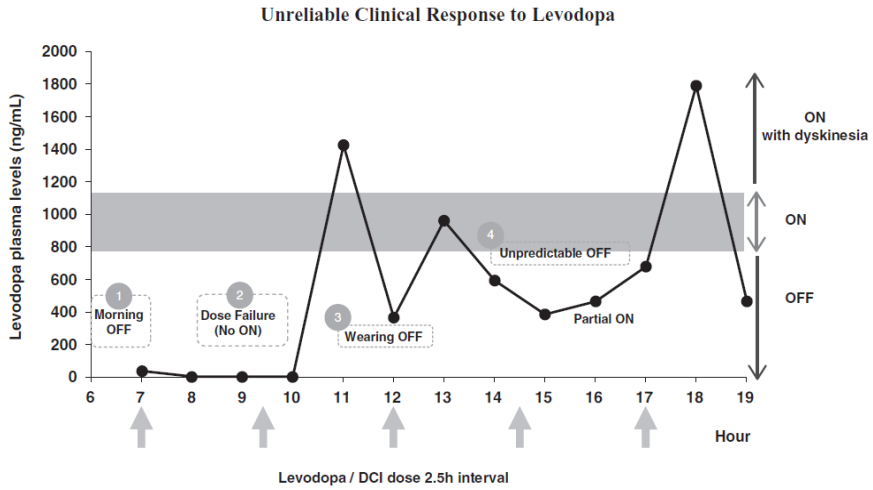
Cynapsus Therapeutics (Form F10)

As such, dosing dynamics for levodopa are challenging (Schapira et al, 2009). Too much drug (or too frequent dosing) leads to leads to dyskinesia, a direct result of excess dopamine in the brain. Too little drug leads to increase "off" time (bradykinesia / akinesia), the specific condition that both Civitas and Cynapsus are aiming to treat.



Source: Schapira et al, 2009

Levodopa also has an unreliable clinical response, marked by dose-by-dose variability in plasma concentrations and the challenging pharmacokinetic profile of the drug (LeWitt PA, 2015). As such, off episodes can be unpredictable and in some cases episodes may be preceded by non-motor symptoms such as pain, tingling, sweating, and anxiety, which can alert patients that motor-impairing symptoms are returning. Off episodes are generally categorized into the following four main types, as shown in the below diagram, which illustrates one patient's response to levodopa over the course of a day.



Source: Based on data and research by Dr. Fabrizio Stocchi.

We are not suggesting Levodopa is not useful drug for the treatment of PD patients. Essentially all patients end up on Levodopa, and treatment significant improves motor dysfunction for a period of time. However, levodopa is associated with dyskinesia at a rate of around 50% of all patients after five years of treatment and 100% after 10 years (Ondo, WG, 2011). And as noted above, treatment with levodopa is challenged by reduced duration of response, unpredictable dose failure, and high dose variability of response.

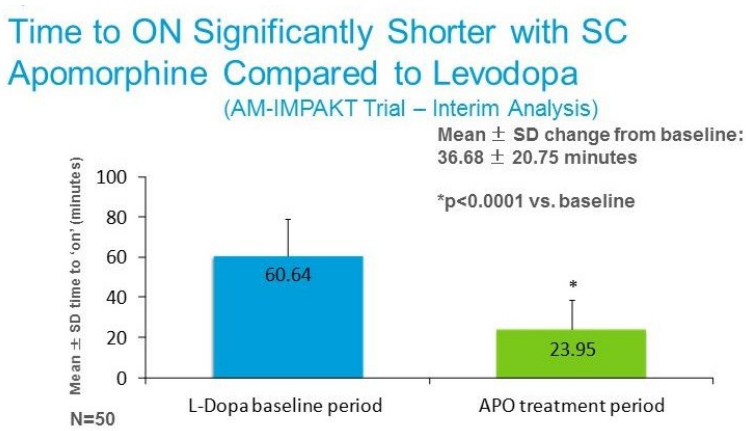
According to work done by Chapuis et al, 2005, wearing off is the most common type of motor fluctuation associated with the long-term use of levodopa, occurring in approximately 80% of levodopa experienced PD patients. Peak-dose dyskinesia is the second most common occurrence, found in roughly 75% of all PD patients. Morning off (also called morning akinesia) and dose failure (paradoxical failure) are also common after long-term levodopa use, occurring in approximately 60% of PD patients. Unpredictable off, while the least common motor fluctuation, still occurs in approximately 35% of all of levodopa experienced PD patients. Clinical data from Cynapsus Phase 2 program shows that APL-130277 works in all four types of off episodes. We believe that patients taking CVT-3011, an inhaled levodopa, will be susceptible to the unpredictable off or dose failure episodes, as well as also be at elevated risk for levodopa-induced dyskinesia.

As such, we question the concept of treating off episodes in Parkinson's patients with more levodopa. Many neurologists and movement disorder doctors will delay the use of levodopa in newly diagnosed Parkinson's patients specifically to avoid the narrowing of the therapeutic window and the risks of complications such as dyskinesia (see this YouTube video from the MJFF talking about Levodopa and off/on time). We believe CVT-301 complicates the dosing regimen for the Parkinson's patient taking a drug like Sinemet-CR. We suspect substantial acceleration of the narrowing of the therapeutic window and dyskinesia with the drug's use. And as the Parkinson's patient progresses from mild to moderate or severe disease, we suspect that CVT-301 will become a less effective drug. We also strongly question the approvability of an inhaled drug, with chronic use, in an elderly population for a non-pulmonary disease. As such, we think the pathway to approval for CVT-301 seems arduous.

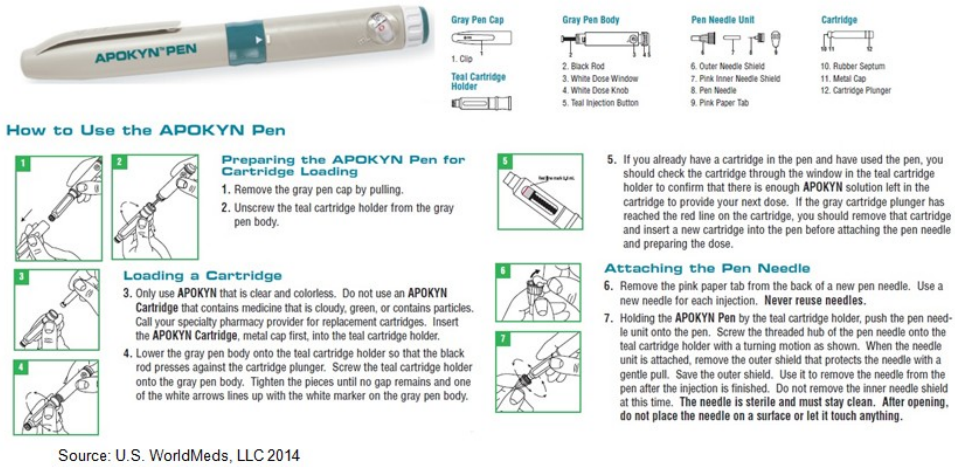
Apomorphine, the active drug in the only currently approved rescue medication for the treatment of off episodes in the U.S. in Apokyn®, is not a dopamine replacement therapy. Apomorphine is a dopamine agonist, and acts directly at the post-synaptic dopamine receptor, thus bypassing the need for dopamine and dopaminergic neurons in the substantial nigra. Instead, apomorphine can act directly on the gabaergic neurons that are not impacted by Parkinson's disease, and provide an effective treatment option as a rescue medication to patients at all stages of disease progression.

The knock on apomorphine is that because the drug is rapidly metabolized by the liver, it must be administered by a route that bypasses the gut. As such, the currently approved formulation of apomorphine in the U.S. is a subcutaneous injection. 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. Apomorphine is highly lipid soluble and quickly crosses the blood-brain barrier. Onset of action is as little as five minutes, but only lasts for 60-90 minutes. Under QID dosing for levodopa, patients with advanced disease may still experience off episodes.

Apomorphine is also far more rapidly active than levodopa. The slide below from Cynapsus investor presentation shows data from the AM-IMPAKT Trial comparing the mean change in baseline "time to on" with oral levodopa vs. subcutaneous apomorphine. Therefore, for all the reasons discussed above, we believe apomorphine is an effective rescue medication for patients experiencing off episodes.

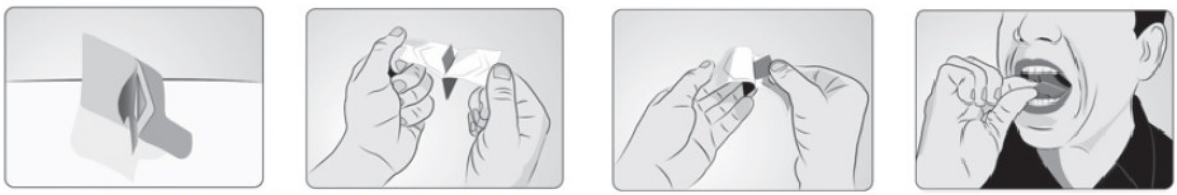


Unfortunately, self-administration of subcutaneous Apokyn is next to impossible for the akinetic (or dyskinetic) Parkinson's patient. For example, the Instructions For Use for Apokyn® is 27 pages long, and consists of steps that logically seem impossible for the frozen or rigid Parkinson's patient to complete. Because self-administration of Apokyn® is nearly impossible, the treatment of "off" episodes requires direct caregiver support, likely from a skilled nurse. There is also titration issued to contend with, as well as injection site-reactions. This places undue burden on the healthcare system.

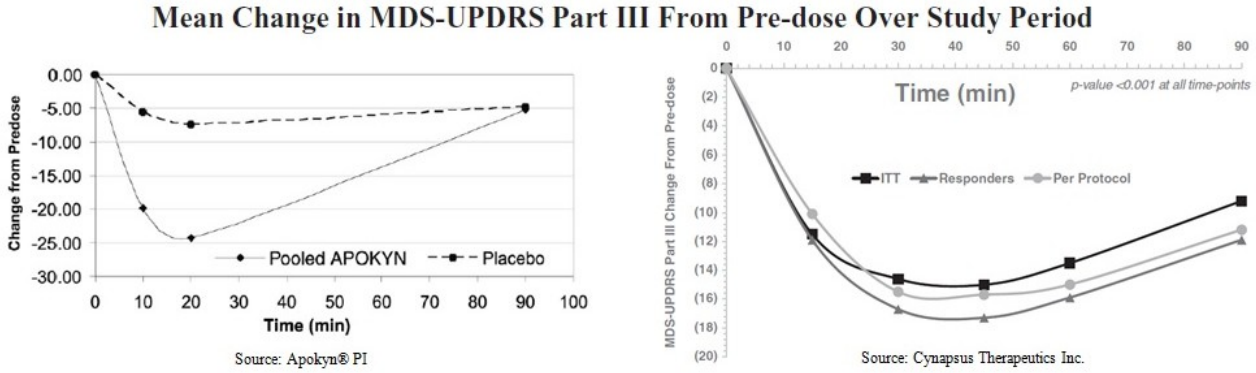


Source: U.S. WorldMeds, LLC 2014

The above inhibiting attributes greatly limit sales of Apokyn in the U.S. Cynapsus' APL-130277 is a sublingual formulation of apomorphine, with each thin film strip found inside an easy to open non-superimposable die cut peelable foil laminate pouch. The product can be self-administered, under the tongue, and is designed to be used anywhere, anytime, with little or no assistance required. Compare the 27 page instructions for use with Apokyn® vs. a cartoon we adapted from Cynapsus prospectus Form F10 below.


Source: Adapted from Cynapsus Therapeutics (Form F10)

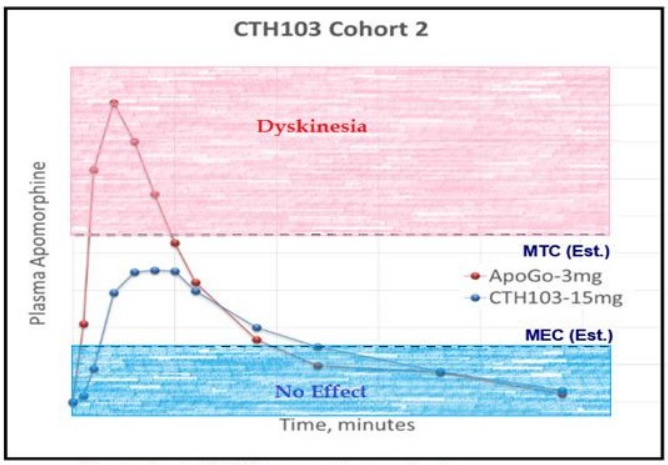
However, beyond the convenience aspect of APL-130277, we believe the drug offers adequate efficacy without significant risk of dyskinesia or injection-site reactions. Below is a graphical representation of the Apokyn® efficacy on the UPDRS scale taken from the drugs prescribing information (left). Compared to pre-dose baseline score, the mean change in score was around -25 at approximately 18 minutes post-dose. The effect of the drug matches that of placebo after 90 minutes. On the right we show the Phase 2 data from Cynapsus' CTH-105 study. The mean change in UPDRS compared to pre-dose baseline on the per protocol basis is -16, with peak effect taking place after 30 minutes.



There are some important aspects of the Cynapsus data that investors need to understand:

- ✓ Firstly, we point investors to the per protocol data because of the 19 patients included in the Phase 2 study, two were given incorrect instructions by the clinical investigator to chew and swallow the film strip. The per protocol data includes the 17 patients dosed correctly. The "responder" analysis includes the 15 of the 17 per protocol patients that achieved clinical on at doses up to 30 mg. Management believes that the two non-responder patients required doses higher than 30 mg to turn on. We note the Phase 3 CTH-300 program will expand to a highest available dose of 35 mg. We also note that 80% of the patients turned on at 20 mg or less, with the mean dose required to convert patients to on being 18.4 mg.

- ✓ Secondly, the effect of the APL-130277 is clearly lower than the subcutaneous injection, with the peak effect for Apokyn® lowering UPDRS by 25 points vs. APL-130277 only lowering UPDRS by 16 points. However, stronger is not necessarily better. Too much drug (apomorphine) can create dyskinesia. The slide below is adapted from peer-reviewed literature taking Cynapsus Phase 1 data from the CTH-103 study showing a "sweet spot" for plasma apomorphine concentration. The plasma concentration needs to be high enough to have effect (minimal effective concentration – MEC) but not so high that it causes side effects (minimal toxic concentration – MTC). Van Laar et al, 1998 concluded that the MEC for apomorphine is roughly 4.7 ng/mL, with dyskinesia generally showing up at concentrations around 8.5 ng/mL. The MTC was found to be 16.7 ng/mL. Therefore, the rounder peak and sustained effect of APL-130277 is likely to cause less dyskinesia or toxic side effects.



Source: Zacks SCR / Cynapsus Therapeutics, Inc.

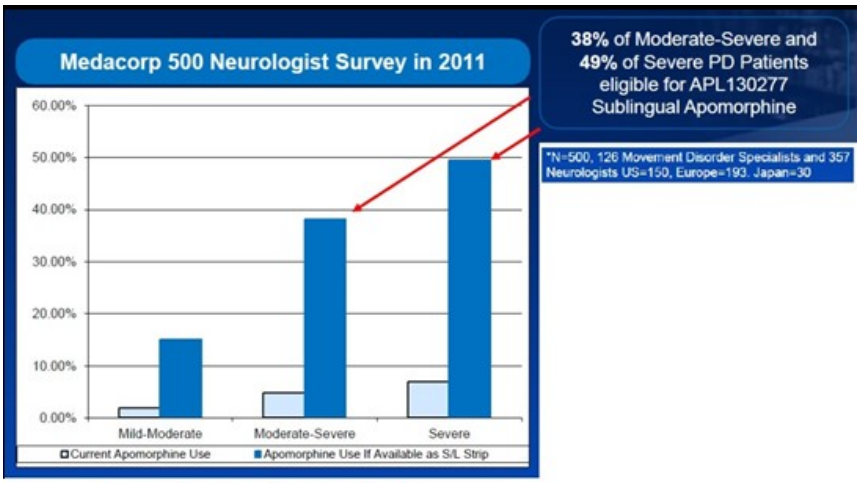
- ✓ Thirdly, the effective onset is slower. However, there are two important points investors must understand about onset and duration: 1) clinically meaningful improvement in motor function was seen in as early as 10 minutes for the majority of patients on APL-130277 and 2) the effect last far longer, with still clinically meaningful effect observed at 90 minutes (end of analysis). So while APL-130277 may not be as rapid acting as Apokyn®, the effect is still fast enough to turn the majority of patients back to on in 10 minutes and the effect is likely long-enough to provide an effective bridge between levodopa dosing (assuming levodopa dosing every 4 hours).

- ✓ Finally, the side effect profile of APL-130277 has been shown to be superior to that of Apokyn® or ApoGo®. For example, based on the Apokyn® label, 26% of patients had injection site reactions, including bruising (16%), granuloma (4%), and pruritus (2%). This does not occur with APL-130277. APL-130277 also does not cause significant oral irritation based on animal data. Based on Phase 2 data from the CTH-104 study, Cynapsus' drug offers far fewer side effects than subcutaneous apomorphine. We believe this is an important aspect of the drug given the patient population and direct competition for treatment options based on dose formulation.

	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.

The comparable dose strength of Apokyn® sells for $13-15 per injection. We believe Cynapsus APL-130277, with a far more convenient administration and lack of skilled caregiver requirement, will see sizable market shares gains and expansion over the current Apokyn market. For example, Cynapsus sponsored neurologist surgery (n=500) with data conclusions suggesting a 7.5-fold increase in penetration across the board for mild, moderate, and severe Parkinson's patients. It is for these reasons that we believe APL-130277 has peak U.S. sales far in excess of Apokyn®, or Acorda's newly acquired CVT-301.



Source: Cynapsus Therapeutics, Inc.

Signs Point To Fundamental Strength

Since we first initiated coverage on Cynapsus in June 2013, management has come a long way in preparing the company for the pending Phase 3 program. Below are several "pieces" put into place or little signs of credibility / validation to the Cynapsus story:

- ✓ Awarded a second grant from the Michael J. Fox Foundation in the sum of $0.5 million to support clinical studies of APL-130277 in July 2014.
- ✓ Raised significant new cash with quality institutional investors in April 2015.
- ✓ Announced the appointment of a Chief Scientific Officer (CSO), Thierry Bilbault, PhD, in October 2014.
- ✓ Announced the appointment of a VP Medical Affairs, Jordan Dubow, M.D., in November 2014.
- ✓ Announced a new board member, Tamar Howson in March 2015.

- ✓ Raised $20 million in new capital in March 2015, with high-quality firms like OrbiMed, Aisling, Venrock, Broadfin, Sphera, Pura Vida, Dafna, and Dexcel Pharma all participating in the offering.
- ✓ Uplisted the shares to the Toronto Stock Exchange in November 2014.
- ✓ Uplist the shares to the NASDAQ in June 2015.
- ✓ Completed U.S. initial public offering lead by Bank of American Merrill Lynch, with potential gross proceeds of $72.45 million assuming full over-allotment.
- ✓ Completed CTH-200 clinical study in December 2015

Conclusion, Valuation & Recommendation

Off time is a significant problem for patients with advanced Parkinson's disease. In the U.S., there are an estimated one million PD patients (4-6 million globally). According to a recent survey by the Michael J. Fox Foundation, more than 90% of PD patients report having off episodes each day. Roughly two-thirds have off time greater than two hours, with 20% experiencing off time of greater than four hours. This is a significant problem for PD patients and has meaningful quality of life impact (see chart below).

A recent paper published by researchers out of the UK on behalf of EUROPAR and EPDA confirms our belief that this is a potential enormous market. The paper concludes that early-morning "off" episodes are a significantly larger problem than believed even five years ago, with nearly two-thirds of all PD patients suffering across all stages of the disease (Rizos et al, 2012). We view this as an enormous unmet medical need.

OFF Episodes Have a Significant Impact on Quality of Life

Significant (p<0.05) impact on PDQ dimension	End of Dose Fluctuations	Nocturnal Akinesia	Early Morning Akinesia	Unpredictable OFFs	Paradoxical Fluctuations
Mobility	X	X	X	X	X
ADL	X	X	X	X	X
Emotional well-being		X			
Stigma	X	X	X	X	X
Social support		X			
Cognition		X			
Communication	X	X	X	X	X
Bodily discomfort		X			
Total score	X	X	X	X	X

Chapuis et al. *Mov Disord* 2005; 20: 224-9.

Data from the recently completed CTH-105 study clearly validates the proof-of-concept for APL-130277. The drug demonstrated clinical signs of efficacy for all doses. Onset of action was as soon as ten minutes for some patients, with mean "time to on" of 22 minutes – admittedly not as rapid as CVT-301 but still well within the reasonable range for a rescue medication. More importantly, duration of effect was still evident at 90 minutes, exceeding what has been demonstrated with Apokyn® or what we suspect will be shown in the CVT-301 Phase 3 trial given the half-life of levodopa has been documented to be less than 90 minutes.

Thanks to recent guidance from the U.S. FDA, the path to the U.S. NDA application has been confirmed and the key registration Phase 3 program is now enrolling patients. If all goes smoothly, we anticipate data from the CTH-300 program in March 2016, with the NDA to be filed before the end of that year.

We see APL-130277 as an easier-to-use and more effective drug than CVT-301, along with a better mechanism of action and pathway to approval. Data from CTH-105 de-risks the story and Cynapsus has enough cash to fund all the necessary clinical trials prior to the U.S. NDA filing.

Management anticipates retaining the global rights to commercialize APL-130277. In the U.S., the company expects to build an in-house sales and marketing team of about 100 reps to effectively market APL-130277 to high-prescribing general neurologists and approximately 1,200 movement disorder specialists. Cynapsus intends to educate both doctors and patients in order to foster a widespread and robust commercial adoption of APL-130277.

Management hopes to initiate pre-market commercialization activates and begin the clinical and regulatory work to bring APL-130277 forward in the EU. This is all designed to improve the attractiveness of the company to a potential pharmaceutical acquirer in 2016 or 2017.

We believe Cynapsus shares are currently worth $30.00. We arrive at this number by projecting peak U.S. sales for the drug in the $680 million range. We assume sales outside the U.S. will total another $400-500 million, all told bringing APL-130277 to approximately a $1.2 billion drug by 2025. We have built two separate valuation models around these sales assumptions, with heavy emphasis on the U.S. market only.

- The first is a forward price-to-sales analysis where we assume 4x peak sales, discounted back to present day at 20%. With a 75% probability of approval this values the company at approximately $550 million.

- The second is a 10-year discounted cash flow analysis projected U.S. and RoW sales to peak, 10% cost of goods sold, 5% residual operating expenses, 26.5% tax rate, and 20% discount rate. With a 75% probability of approval this values the company at approximately $505 million.

On a fully diluted basis, our $30.00 target equates to an enterprise value of approximately $485 million. We suspect that the company will still hold $30+ million in cash on hand at the end of 2016. We remind investors that Acorda paid $525 million for Civitas in 2014, Pfizer acquired Nextwave in 2012 for up to $700 million, and Lundbeck acquired Chelsea Therapeutics for $658 million in 2014. With the NDA under review, it would not surprise us one bit to see Cynapsus acquired for between $500 and $750 million. This range would equate to a 3+ fold increase in price for Cynapsus shareholders as of today.

FINANCIAL MODEL

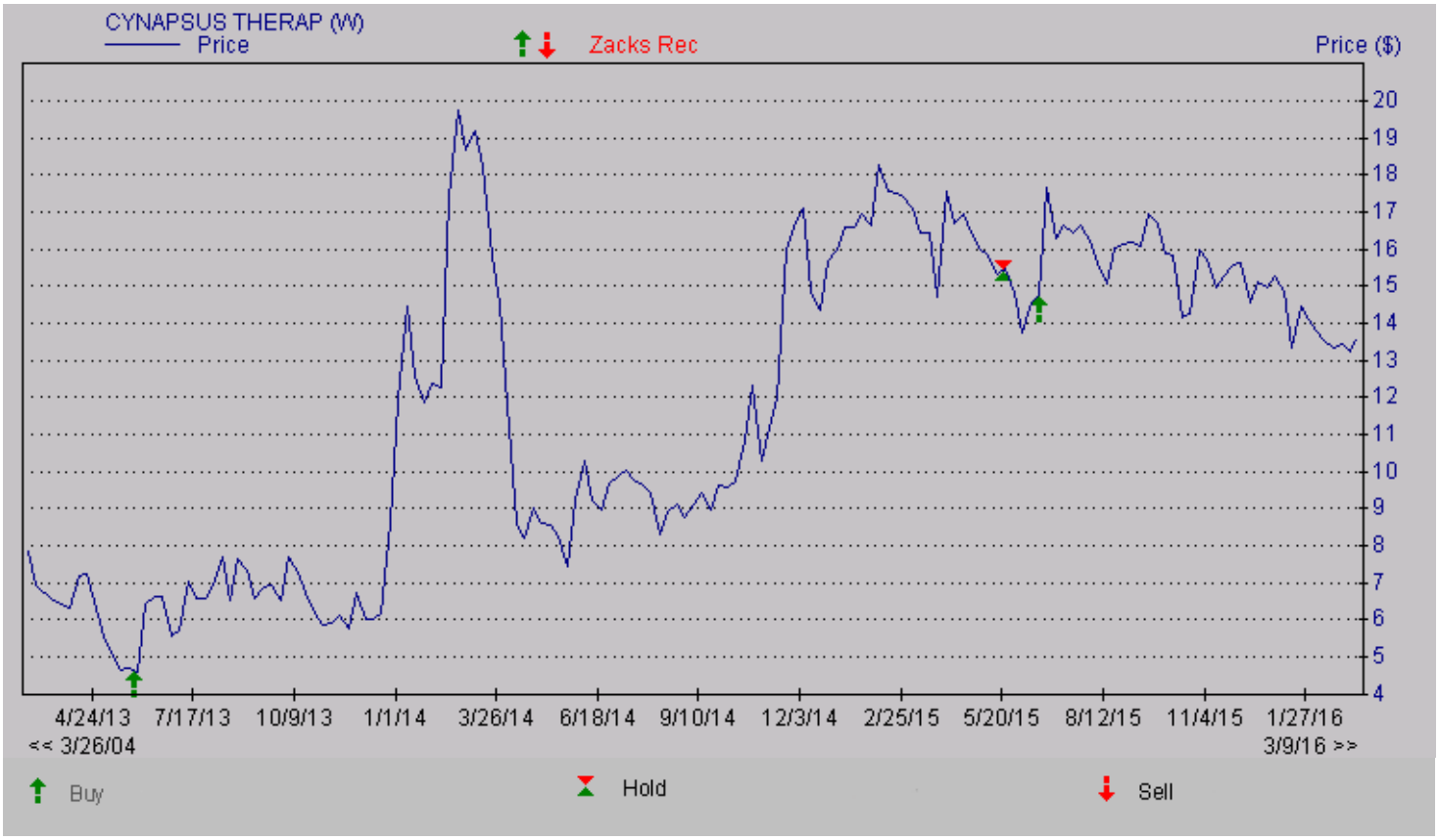
Cynapsus Therapeutics – Income Statement (Canadian Dollars)

Cynapsus Therapeutics Inc.	2014 A	2015 A	Q1 E	Q2 E	Q3 E	Q4 E	2016 E	2017 E
APL-130277 WW Sales	$0	$0	$0	$0	$0	$0	$0	$0
Royalty Payments	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-	-
Licensing & Collaborative	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-	-
Total Revenues	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-	-
Cost of Sales	$0	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	-	-	-	-	-	-	-	-
Operating, General & Admin	$5.01	$11.38	$3.90	$4.00	$4.20	$4.50	$16.60	$18.30
Research & Development	$6.19	$27.40	$8.70	$7.20	$8.20	$9.30	$33.40	$37.50
Share-Based Comp	$0.98	$1.50	$0.50	$0.75	$0.40	$0.35	$2.00	$2.50
Amortization & Depreciation	$0.22	$0.00	$0.05	$0.05	$0.05	$0.05	$0.20	$0.00
Foreign Exchange	($0.69)	($12.79)	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Other Expenses	($0.09)	($0.02)	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Operating Income	($11.61)	($27.47)	($13.15)	($12.00)	($12.85)	($14.20)	($52.20)	($58.30)
Operating Margin	-	-	-	-	-	-	-	-
Grants & Other Income	$0.69	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Interest / Financing Net	$0.05	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Pre-Tax Income	($10.82)	($27.47)	($13.15)	($12.00)	($12.85)	($14.20)	($52.20)	($58.30)
Income Taxes Paid	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Tax Rate	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*
Net Income	($10.82)	($27.47)	($13.15)	($12.00)	($12.85)	($14.20)	($52.20)	($58.30)
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**($2.56)**	**($2.98)**	**($1.07)**	**($0.96)**	**($1.01)**	**($1.09)**	**($4.13)**	**($4.16)**
YOY Growth	-	-	-	-	-	-	-	-
Basic Shares Outstanding	4.2	9.2	12.3	12.5	12.7	13.0	12.6	14.0

Source: Zacks Investment Research, Inc. *Anita Dushyanth, PhD*

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