Zacks Small-Cap Research

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Cynapsus Therapeutics (CYNA-NASDAQ)

CYNA: Cynapsus Snags Fast Track Designation for APL-130277 To Treat Parkinson's Disease

Our 10-year discounted cash flow analysis projected U.S. and RoW sales, with 20% discount rate and a 75% probability of approval values the company at approximately $706 million.

OUTLOOK

Cynapsus Therapeutics Inc. (CYNA) exited Q2 2016 with a solid cash balance of about $55 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.

Current Price (08/29/16)	$18.51
Valuation	**$38.00**

SUMMARY DATA

52-Week High	**$19.25**
52-Week Low	**$11.16**
One-Year Return (%)	**14.47**
Beta	**0.77**
Average Daily Volume (sh)	**69,560**
Shares Outstanding (mil)	**12**
Market Capitalization ($mil)	**$228**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**60**
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 2016 Estimate	**-6.1**
P/E using 2017 Estimate	**-5.6**
Zacks Rank	**N/A**

Risk Level	**Above Avg.,**
Type of Stock	**Small-Blend**
Industry	**Med-Drugs**

ZACKS ESTIMATES

Revenue
(in millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2014	$0.0A	$0.0A	$0.0A	$0.0A	$0.0A
2015	$0.0A	$0.0A	$0.0A	$0.0A	$0.0A
2016	$0.0A	$0.0E	$0.0E	$0.0E	$0.0E
2017					$0.0E

Price/Sales Ratio (Industry = 2.5x)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2014	-$0.48 A	-$0.64 A	-$0.32 A	-$1.12 A	-$1.92 A
2015	-$0.64 A	-$1.22 A	$0.18 A	-$0.75 A	-$2.45 A
2016	-$0.68 A	-$0.83 A	-$0.75 E	-$0.81 E	-$3.05 E
2017					-$2.90 E

Zacks Projected EPS Growth Rate - Next 5 Years % **N/A**

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WHAT'S NEW

CYNA: Cynapsus Snags Fast Track Designation for APL-130277 To Treat Parkinson's Disease (PD)

There has been a series of positive news flow from CYNA since our previous update.

In mid-August 2016, the company announced that after reviewing the safety data from CTH-300 and CTH-301 clinical trials, the Data Safety and Monitoring Board (DSMB) recommended to continue the CTH-300 trial as planned. Additionally, the study was amended to allow for at-home titration, after the patient's initial visit to the clinic. There may be several health and economic benefits from treatments administered at home, such as the reduction in healthcare service costs and waiting times. The at-home treatment option increases convenience and for PD patients to treat their OFF episodes which may consequently improve patient compliance. Further, it allows for assessment of results in a real-world setting.

Today (August 29, 2016) the company announced that the FDA has granted Fast Track Designation for APL-130277. The Fast Track program was put into place under the FDA Modernization Act of 1997. The Fast Track designation allows expedited review of new drugs that are intended to treat serious conditions as well as demonstrate the potential to address an unmet medical need. The designation allows CYNA to have a rolling review with the FDA during the submission process and this is because the Fast Track designation allows the following:

- Frequent communication (written/in-person meeting) with the FDA to discuss the clinical development plan and trial design for the drug
- Relaying relevant data to support drug approval
- Eligibility for an accelerated approval and priority review, including the submission of a New Drug Application (NDA) on a rolling basis. This implies that CYNA can submit those sections of an NDA that are completed, to be reviewed by the FDA, instead of waiting to complete every section and then submit the entire application for review.

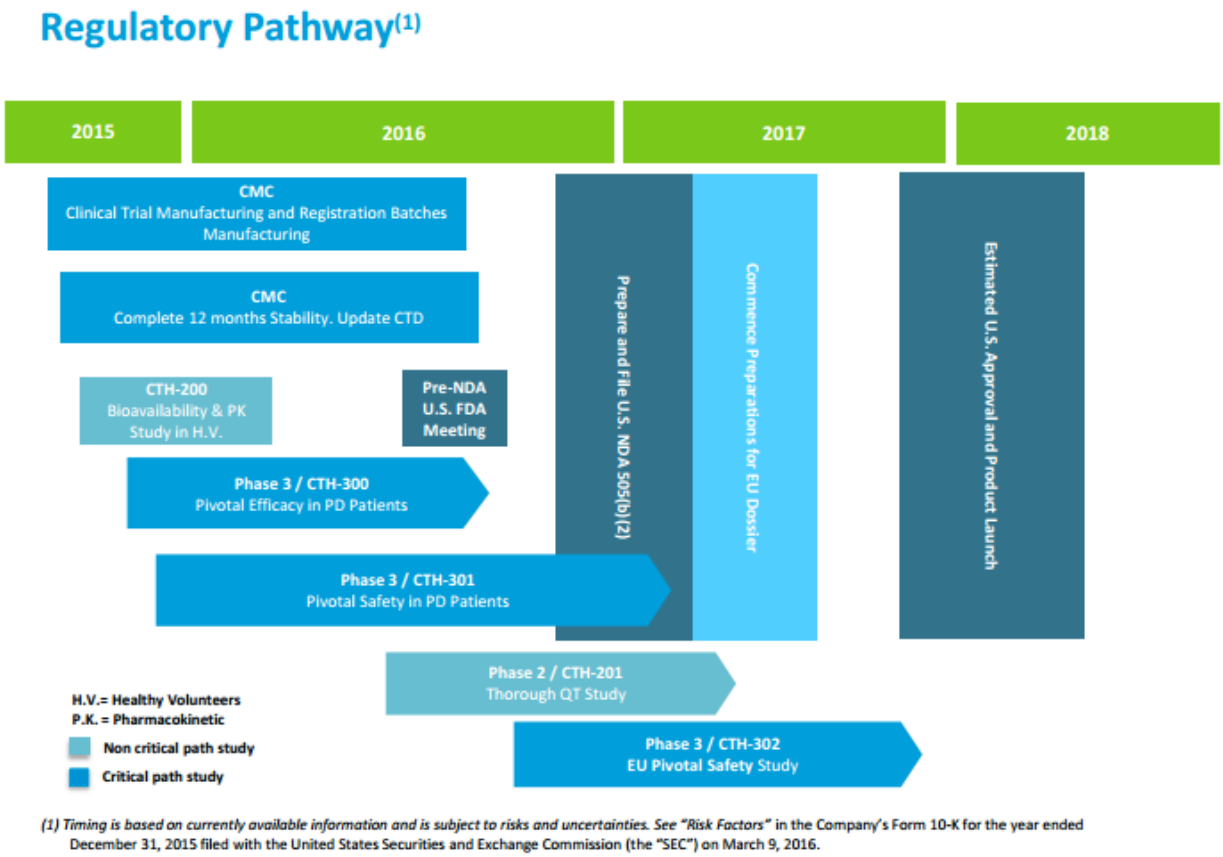
Currently, PD has very few therapeutic options that work and the treatment typically given is Sinemet® (Carbidopa/Levodopa). While apomorphine has been the holy grail in treating advanced PD patients, the high cost of the drug, the necessity of co-therapies for prevention of side effects and the subcutaneous administration has restricted its use. The sublingual formation of APL-130277 is attractive as it is definitely user friendly and less painful as compared to the injectable drug. CYNA had shown compelling clinical data of APL-130277 in PD and therefore, regulators were convinced to approve the fast-track status. The Fast Track program allows frequent communication between the FDA and management to ensure proper execution of the clinical trials to gather relevant data.

Cynapsus also provided update on completion timelines for their clinical trials. Based on patient visit schedules, post the dose titration phase, top line data for the Phase 3 Efficacy trial CTH-300 is expected in mid-to-late fourth quarter of 2016. Furthermore, the CTH-201 Phase 2 Thorough QT study, is expected to commence in the fourth quarter of 2016, and is planned to be completed in the first half of 2017.

European Clinical Trial Update: As planned the company consulted with the European Medicines Agency (EMA) in mid-July 2016 regarding the design, duration and size of the clinical trial for obtaining regulatory approval in Europe. The EMA requires that the trial is able to establish significant functional endpoint (activities of daily living) as compared to SC apomorphine. Based on the guidance received from the EMA, Cynapsus plans to initiate a pivotal clinical program evaluating the safety and efficacy of APL-130277 in up to eighty PD patients in Europe in the fourth quarter of 2016. Patients are expected to be randomized in a 4-week open label, active comparator crossover study with sub-cutaneous apomorphine. The functional endpoints include the duration of ON state, preference and ease-of-use of APL-130277, the use of patient diaries, and tolerability of APL-130277. The study expects using limited use of an anti-emetic (domperidone). Although domperidone (upper gastrointestinal motility agent) has been used previously in Europe to reduce occurrence of peripheral adverse events such as nausea and vomiting, its use was restricted to a low dose of 10mg for three times a day up to one week duration. CYNA has been advised to restrict the use of antiemetic in this study as it may cause sedation or drowsiness and/or reduce the

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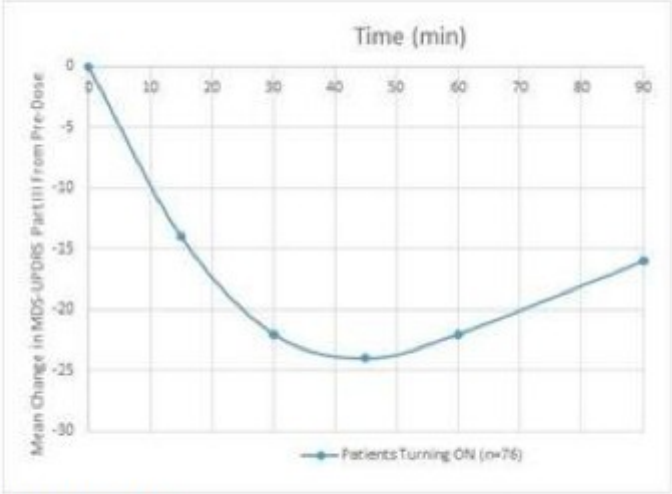
effectiveness of APL-130277. Based on the current timing of events, the European clinical trial is expected to commence in the fourth quarter of 2016.



(Source: www.cynapsus.ca)

CTH-300 Phase 3 Efficacy Study: This double-blind, placebo-controlled, parallel-design trial across 35 sites 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 were enrolled into the study. Patients were dosed at home as well as in the clinic. They were observed for 12 weeks and evaluated every four weeks. The primary endpoint 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. At the end of June 2016 Cynapsus announced that the last patient had been enrolled into the study. The results of the dose titration phase from the first 92 patients were released on July 19, 2016. The company anticipates releasing top-line data before end of Q4 2016.

The following points highlight the results from the dose titration phase. As a reminder, the primary endpoint is the mean change in MDS-UPDRS Part III score (changes/improvement in motor function) before and after treatment and the secondary endpoint is the percentage of patients that go from OFF to complete ON state in thirty minutes at week twelve after taking APL-130277.



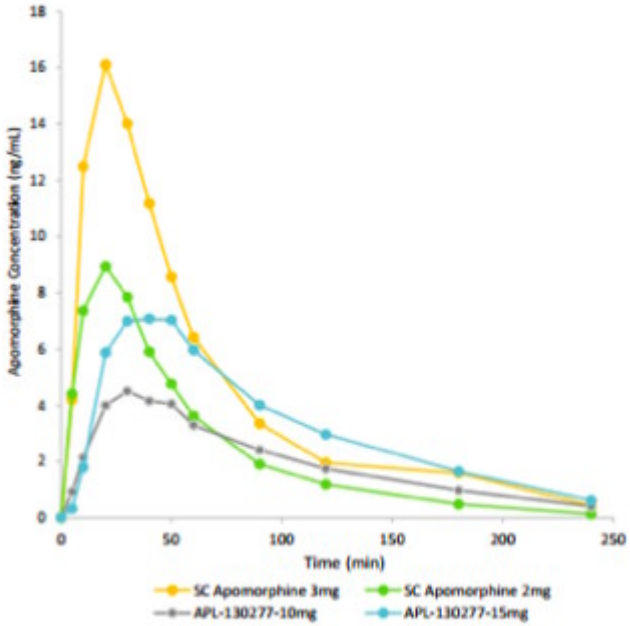
(Source: www.cynapsus.ca)

- The median dose of APL-130277 that helped patients to turn to complete ON state was 20mg.
- 83% of patients turned from OFF to fully ON state.
- 78% of patients turned fully ON within 30 minutes; about 38% were fully ON at 15 minutes.
- The mean change in MDS-UPDRS Part III score was 22 points from baseline to 30 minutes and 24 points from baseline to 45 minutes. A low rating indicates an improvement after treatment.

N=92	Number of Patients with an Adverse Event			
	Any AE	Mild AE	Moderate AE	Severe AE
	N (%)	N (%)	N (%)	N (%)
Nausea	15 (16)	12 (13)	2 (2)	1 (1)
Dizziness	7 (8)	4 (4)	3 (3)	0 (0)
Somnolence	4 (4)	3 (3)	1 (1)	0 (0)
Yawning	3 (3)	3 (3)	0 (0)	0 (0)
Vomiting	2 (2)	1 (1)	1 (1)	0 (0)
Symptomatic Hypotension	1 (1)	1 (1)	0 (0)	0 (0)
Stomatitis/ Irritation	0 (0)	0 (0)	0 (0)	0 (0)

(Source: www.cynapsus.ca)

- Between five to twelve minutes after dosing about 60% of patients showed improvement in motor function.
- Patients demonstrated improvement in motor function lasted more than ninety minutes. The mean improvement of the MDS UPDRS Part III score was sixteen points.
- APL-130277 was well tolerated. About 34% of patients reported adverse events such as mild nausea (16%), dizziness (8%), somnolence (4%), vomiting (2%) and symptomatic hypotension (1%).
- No one reported having local irritation during the study.
- A total of sixteen patients were dosed and did not complete the dose titration study. Five patients discontinued due to an adverse event, nine patients discontinued as the highest dose in this study (35mg) was not sufficient to turn them from OFF to ON state within the 45-minute duration and two patients discontinued for administrative reasons.



CTH-103 Study (Source: www.cynapsus.ca)

The Phase 1 clinical trial (CTH-103) demonstrated that APL-130277 had a pharmacokinetic (PK) profile that was comparable to SC apomorphine. APL-130277 demonstrated muted adverse events (AEs) including nausea, vomiting, hypotension and skin irritation profile. The rounded curve on the graph showing plasma concentration and longer duration of effect compared to SC apomorphine (blue) shows extended efficiency of APL-130277. The findings from CTH-300 dose titration phase were comparable to those from CTH-103 study.

Management thinks that the trial is adequately powered (90%) with a sample size of 92 patients and is sufficient to show statistical and clinical significance. Further, the Phase 3 study has almost five times more patients from various centers distributed widely with a broad range of investigators as compared to Phase ½ studies. This helps prove the efficacy of the drug across a wider population that may help in highlighting the superiority of the drug relative to the active comparator.

The CTH-301 Phase 3 Safety Study (CTH-301) is a long-term open-label, single arm safety study in PD patients who have at least one OFF episode per day, with total OFF time of at least two hours per day. The objective is to evaluate the safety and tolerability of APL-130277 in up to 200 patients with PD over a six-month period. Patients completing CTH-300 are eligible to enter CTH-301. In addition, new patients from approximately 65 sites in the U.S. and Europe will be enrolled in CTH-301.

Market Potential and Pricing: Approximately one million of the U.S. adult population and an estimated six million people worldwide suffer from PD. Management's survey conducted in 2012 provided insight into the market potential of this product. About 40% of these patients experience at least one OFF episode or two hours of cumulative OFF episodes per day. This equates to a target patient population of around 400,000. As per management's survey of neurologists and movement disorder specialists, the target audience can be categorized into three segments: ~20% are considered mild (experiencing one OFF episode per day), ~55% are considered moderate (experiencing two OFF episodes per day) and ~25% are considered advanced (experiencing three or more OFF episodes per day).

Cynapsus is attempting to address the wide range of severity of PD patients (mild, moderate and severe) with APL-130277. Since every PD patient's range of symptoms is unique they require different treatment regimens. While patients with mild symptoms may administer one strip per day, a patient experiencing severe symptoms may require three to five strips per day. Further, PD is known to worsen over time, which implies that increased doses need to be taken to manage symptoms as they progress. Additionally, high insurance premium are imposed on patients taking expensive drugs.

In order to address this broad spectrum of patient audience and bring financial relief them, CYNA is planning to price APL-130277 attractively to make it accessible and affordable. While apomorphine has been the holy grail in treating advanced PD patients, the high cost of the drug, the necessity of co-therapies for prevention of side effects

and the subcutaneous administration has restricted its use. Besides attracting new patients to the sublingual formation, APL-130277 could widen the use per patient as it is definitely user friendly and less painful as compared to the injectable drug.

Back in 2010-2011, management surveyed neurologists, movement disorder specialists as well as large insurance payors to determine pricing structure for the drug. The result of the survey showed a potential favorable pricing environment and high acceptance (~90%) for reimbursement. Roughly 75% of the responders were willing to reimburse at an average wholesale price equal to the apomorphine injection, if clinical trials demonstrated substantial benefit over the injectable apomorphine.

It is a known fact that apomorphine is a morphine derivative but is a non-narcotic. It acts as a potent dopaminergic agonist. Since hepatic metabolism prevents its effectiveness when dosed orally, subcutaneous (SC) injection has been set as the gold standard for maximum effectiveness. SC injections are used either intermittently or continuously to help in managing sudden and/or unexpected OFF episodes. Since the use of injections can be difficult for some patients experiencing severe tremor or dyskinesias during OFF periods CYNA has developed APL-130277 that is dosed sublingually.

Cash Position: As of August 11, 2016, CYNA reported cash and cash equivalents of approximately $55 million. Quarterly operating burn is ~$8 million. There are currently 16.5 million shares on a fully diluted basis. CYNA also has some warrants that are subject to a forced exercise provision if the firm's closing share price meets or exceeds the strike price. We believe there is a potential for this to happen when the firm releases top line data from CTH-300 study as well as if interim results are revealed from the European trial by end of 2016/beginning 2017. If all of the warrants are exercised, CYNA will receive proceeds of about $30 million (non-dilutive to investors) which will bring the cash balance to around $70 million in the beginning of 2017. The additional funds will be used for launching APL-130277 and for general working capital. We have forecasted NDA approval around the beginning of 2018. Based on our financial model, we believe this is achievable with ~$25 million in cash on hand at that time.

- ☑ **Q2 2016 –** Posters at the American Academy of Neurology Meeting in Vancouver, British Columbia
- ☐ **Q2 2016** - Meet with European Medicines Agency
- ☐ **H2 2016** - European registration study to commence
- ☐ **H2 2016 –** Thorough QT study to commence
- ☐ **Q2/Q3 2016** - Top-line data from CTH-300 Phase 3 efficacy registration study
- ☐ **Q4 2016/Q1 2017** - Top-line data from CTH-301 Phase 3 safety registration study
- ☐ **End 2016/Early 2017** - File New Drug Application with U.S. FDA
- ☐ **H1 2017 –** Commence preparations for EU dossier
- ☐ **End 2017/Early 2018 –** Estimated U.S. approval and product launch

(Source: www.cynapsus.ca)

Anticipated Timeline: CYNA's goal is to report data from the CTH-300 study in the fourth quarter 2016. If the data are positive, which we think is highly likely, we believe the company will move quickly to secure a commercialization partnership for the drug. This could be a potential game-changer for Cynapsus, which will allow management to initiate additional M&A or licensing transactions to expand their commercial business beyond 2018.

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

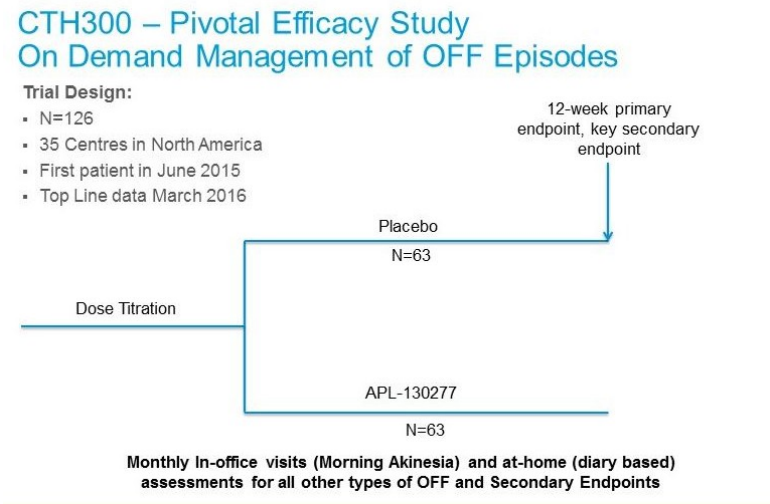
The basic share count is at roughly 12.1 million. The fully-diluted share count, which includes approximately 3.3 million warrants will be approximately 15.4 million. The basic market capitalization of the NASDAQ-listed shares is approximately $183 million ($233 million fully-diluted). Our financial 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 double-blind, placebo-controlled, parallel-design trial (NCT02469090) across 35 sites commenced during Q2 2015 (June 2015) to evaluate the efficacy and safety of APL-130277 versus placebo in 102 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 were enrolled into the study. Patients were dosed at home as well as in the clinic. They were observed for 12 weeks and evaluated every four weeks. The primary endpoint 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. At the end of June 2016 Cynapsus announced that the last patient had been enrolled into the study. As anticipated, the company released dose titration results from this study in July 2016 and top-line data are expected by end of 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 102 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 completes 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.

As planned the company consulted with the European Medicines Agency (EMA) regarding the design, duration and size of the clinical trial for obtaining regulatory approval in Europe. The EMA requires that the trial is able to establish significant functional endpoint (activities of daily living) as compared to SC apomorphine. Based on the guidance received from the EMA, Cynapsus plans to initiate a pivotal clinical program evaluating the safety and efficacy of APL-130277 in up to eighty PD patients in Europe in 2H 2016. Patients are expected to be randomized in a 4-week open label, active comparator crossover study with sub-cutaneous apomorphine. The functional

endpoints include the duration of ON state, preference and ease-of-use of APL-130277, the use of patient diaries, and tolerability of APL-130277. The study expects using limited use of an anti-emetic (domperidone). Although domperidone (upper gastrointestinal motility agent) has been used previously in Europe to reduce occurrence of peripheral adverse events such as nausea and vomiting, its use was restricted to a low dose of 10mg for three times a day up to one week duration. CYNA has been advised to restrict the use of antiemetic in this study as it may cause sedation or drowsiness and/or reduce the effectiveness of APL-130277. Based on the current timing of events, the European clinical trial (CTH-302: European Registration Study) is expected to commence in the fourth quarter of 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

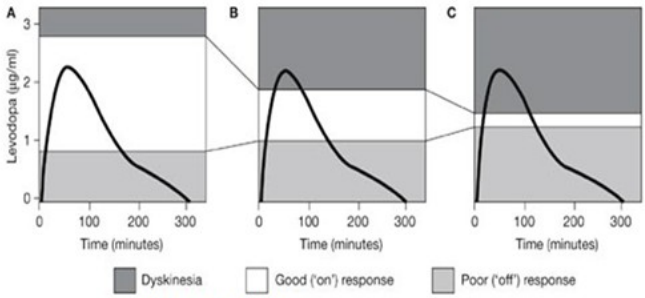
$500 million, consistent with what we believe and model. Civitas had been previously planning an initial public offering, but the $525 million all-cash offer from Acorda was simply too attractive to pass up.

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.

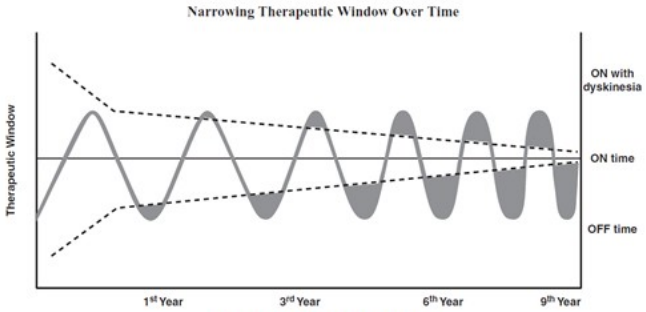
The administration of levodopa temporarily diminishes the motor symptoms associated with the lack dopamine in the substantia nigra. Carbidopa, a dopa decarboxylase inhibitor, is commonly dosed with levodopa to prevent L-DOPA metabolism before it reaches the blood-brain barrier. In fact, co-formulations 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).

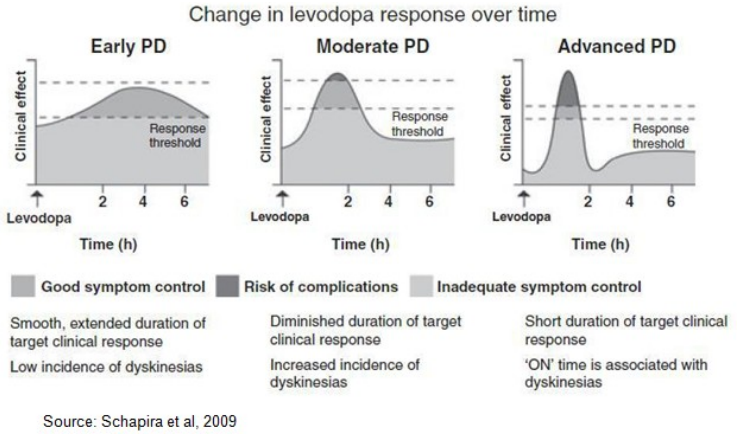


Source: Olanow CW et al, 2006
A: Naïve patient, B: Experienced patients, C: Severe PD patient



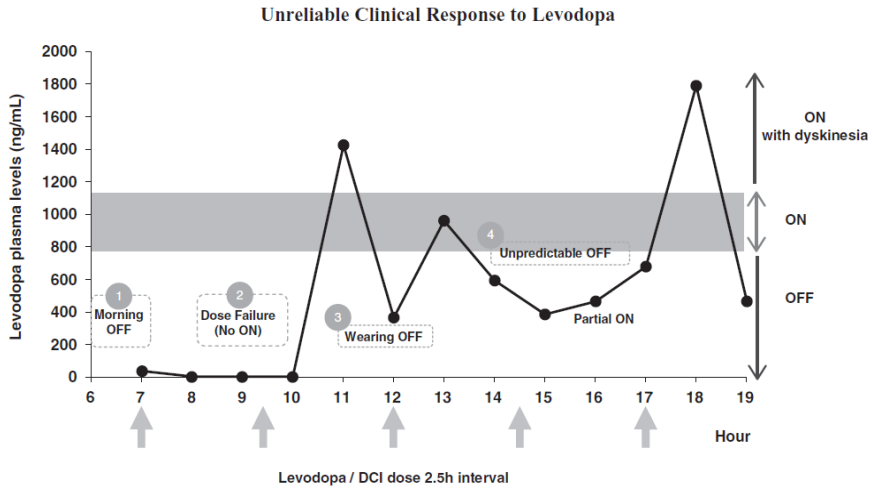
Cynapsus Therapeutics (Form F10)

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.

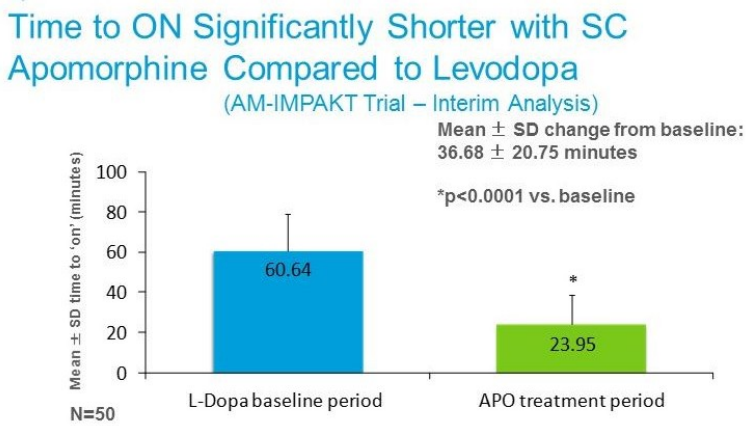
As such, we question the concept of treating off episodes in Parkinson's patients with more levodopa. Many neurologists and movement disorder doctors will delay the use of levodopa in newly diagnosed Parkinson's patients specifically to avoid the narrowing of the therapeutic window and the risks of complications 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.

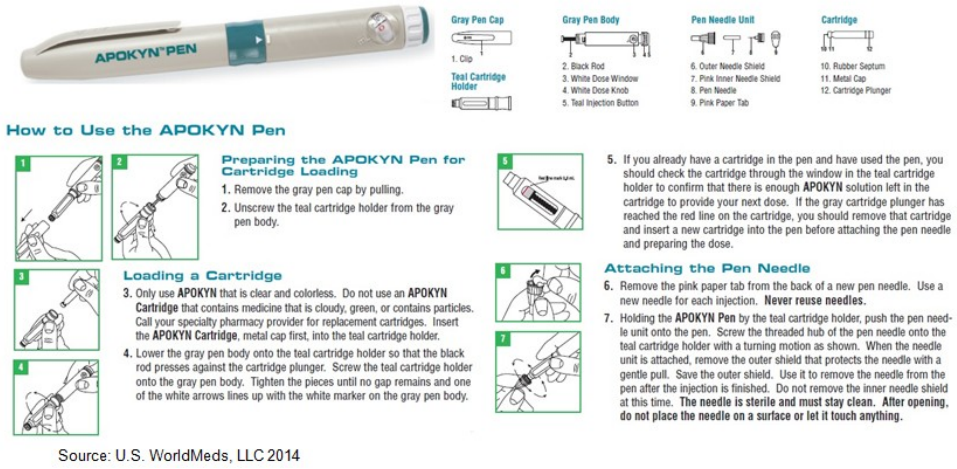
Apomorphine, the active drug in the only currently approved rescue medication for the treatment of off episodes in the U.S. in Apokyn®, is not a dopamine replacement therapy. Apomorphine is a dopamine agonist, and acts directly at the post-synaptic dopamine receptor, thus bypassing the need for dopamine 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.

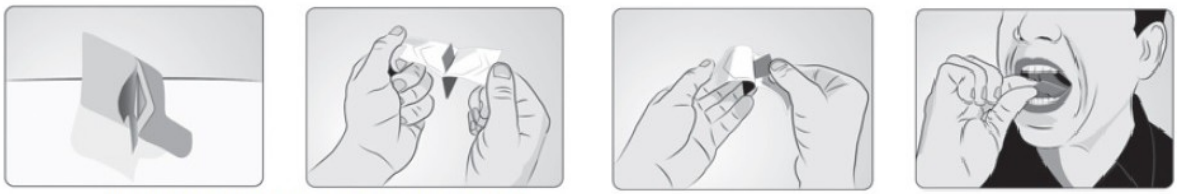


Unfortunately, self-administration of subcutaneous Apokyn is next to impossible for the akinetic (or dyskinetic) Parkinson's patient. For example, the Instructions For Use for Apokyn® is 27 pages long, and consists of steps that logically seem impossible for the frozen or rigid Parkinson's patient to 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.



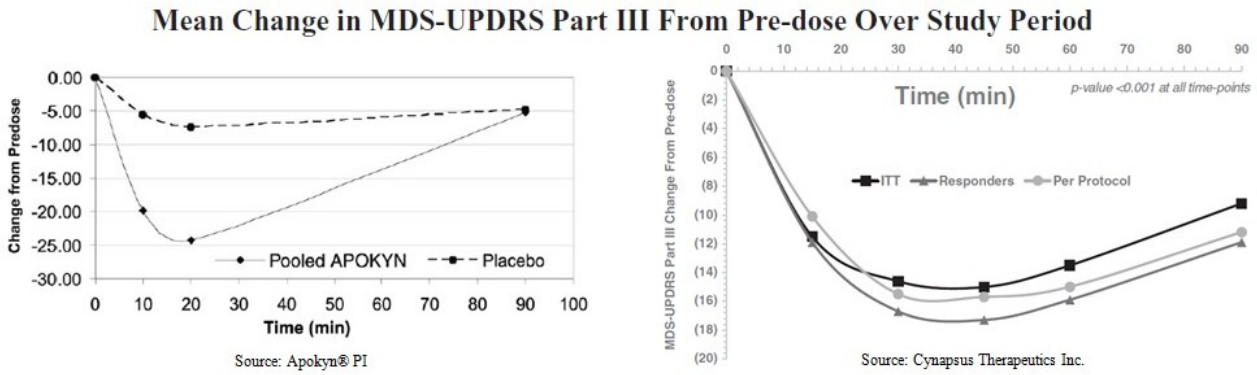
Source: U.S. WorldMeds, LLC 2014

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.



Source: Apokyn® PI

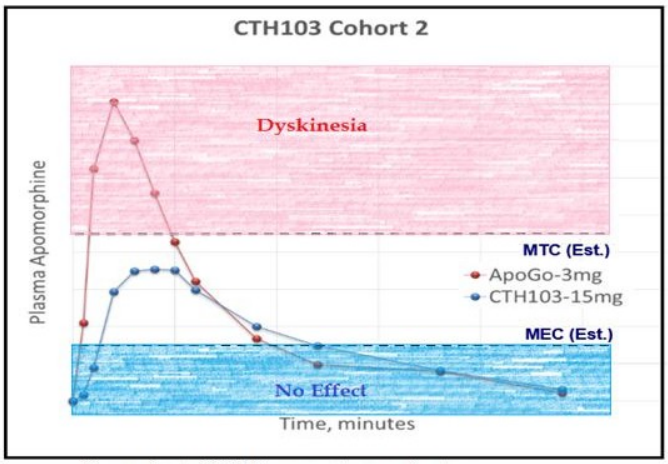
Source: Cynapsus Therapeutics Inc.

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.

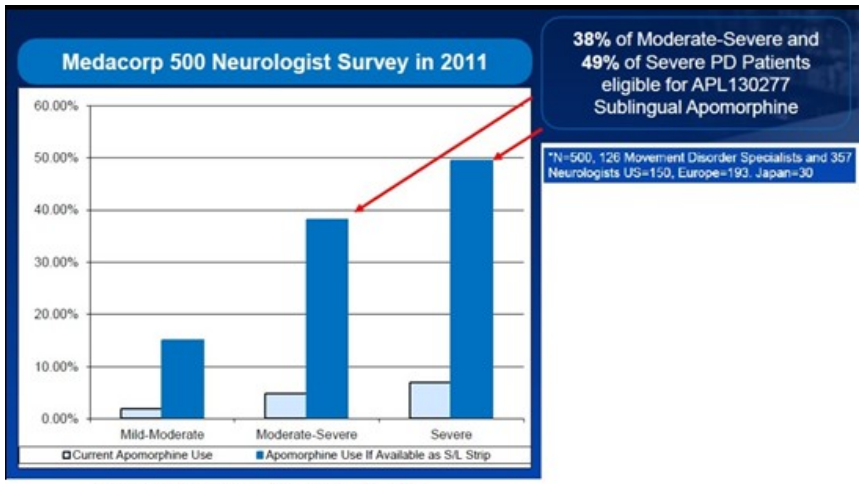
	S.C 2mg (n=15)	APL 10mg (n=15)	S.C 3mg (n=14)	APL 15mg (n=14)
# of subjects with AEs	9	5	14	7
# of subjects with Moderate AEs	5	2	10	3

Source: Cynapsus Therapeutics, Inc.

The comparable dose strength of Apokyn® sells for $100-150 per injection[1]. 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

[1] www.bsneny.com/content/neny_prov_guid_Apokyn.pdf

(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.
- ✓ Uplisted the shares to the Toronto Stock Exchange in November 2014.
- ✓ 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.
- ✓ 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.
- ✓ Beefed-up their leadership team in 2015 and 2016
- ✓ Completed patient enrollment in Pivotal Phase 3 Efficacy Trial (CTH-300) of APL-130277 in June 2016

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 Q4 2016, with the NDA to be filed during end 2016/beginning 2017 timeframe.

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 $38.00. 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, 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 $706 million.

On a fully diluted basis, our $38.00 target equates to an enterprise value of approximately $627 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.

PROJECTED INCOME STATEMENT

Cynapsus Therapeutics Inc.	2015 A	Q1 A	Q2 A	Q3 E	Q4 E	2016 E	Q1 E	Q2 E	Q3 E	Q4 E	2017 E
APL-130277 WW Sales	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0
Royalty Payments	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-	-	-	-	-
Licensing & Collaborative	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-	-	-	-	-
Total Revenues	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-	-	-	-	-
Cost of Sales	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	-	-	-	-	-	-	-	-	-	-	-
Operating, General & Admin	$11.38	$3.14	$2.70	$3.15	$3.30	$12.29	$3.40	$3.10	$3.50	$3.80	$13.80
Research & Development	$27.40	$5.22	$7.15	$6.40	$7.25	$26.02	$5.80	$6.30	$6.00	$7.30	$25.40
Share-Based Comp	$1.50	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Amortization & Depreciation	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Foreign Exchange	($12.79)	($0.00)	($0.01)	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Other Expenses	($0.02)	$0.00	$0.33	$0.00	$0.00	$0.00	$0.00	$0.33	$0.00	$0.00	$0.00
Operating Income	($27.47)	($8.36)	($10.17)	($9.55)	($10.55)	($38.31)	($9.20)	($9.73)	($9.50)	($11.10)	($39.20)
Operating Margin	-	-	-	-	-	-	-	-	-	-	-
Grants & Other Income	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Interest / Financing Net	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Pre-Tax Income	($27.47)	($8.36)	($10.17)	($9.55)	($10.55)	($38.31)	($9.20)	($9.73)	($9.50)	($11.10)	($39.20)
Income Taxes Paid	$0.00	$0.00	$0.00	$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%*	*35%*	*35%*	*35%*
Net Income	($27.47)	($8.36)	($10.17)	($9.55)	($10.55)	($38.31)	($9.20)	($9.73)	($9.50)	($11.10)	($39.20)
Net Margin	-	-	-	-	-	-	-	-	-	-	-
Reported EPS	**($2.98)**	**($0.68)**	**($0.83)**	**($0.75)**	**($0.81)**	**($3.05)**	**($0.70)**	**($0.72)**	**($0.69)**	**($0.81)**	**($2.90)**
YOY Growth	-	-	-	-	-	-	-	-	-	-	-
Basic Shares Outstanding	9.2	12.3	12.3	12.7	13.0	12.6	13.2	13.5	13.7	13.7	13.5

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

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