

**FORM 51-102F3**

**MATERIAL CHANGE REPORT**

**Item 1 - Name and Address of Company:**

Cynapsus Therapeutics Inc.  
828 Richmond Street West  
Toronto, Ontario M6J 1C9

(the “Corporation”)

**Item 2 - Date of Material Change:**

November 19, 2014.

**Item 3 - News Release:**

A news release was issued on November 19, 2014, a copy of which is annexed hereto as Schedule “A”.

**Item 4 - Summary of Material Change:**

Cynapsus Therapeutics Inc. (CTH: TSX-V) (CYNAF: OTCQX), a specialty pharmaceutical company focused on Parkinson’s disease, today announced positive top-line results from its CTH-105 Phase 2 clinical trial of APL-130277 for the management of OFF motor symptoms of Parkinson’s disease.

**Item 5 - Full Description of Material Change:**

See attached news release.

**Item 6 - Reliance on Subsection 7.1(2) or (3) of National Instrument 51-102**

Not Applicable.

**Item 7 - Omitted Information:**

Not Applicable.

**Item 8 -**

**Executive Officer:**

For further information, please contact:

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Chief Operating Officer / Chief Financial Officer  
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Telephone: (416) 703-2449 (ext. 253)

**Item 9 -**

**Date of Report:**

DATED at Toronto, Ontario, this 19<sup>th</sup> day of November, 2014.

## **SCHEDULE "A"**

### **PRESS RELEASE**

#### **Cynapsus Therapeutics Announces Positive Top-Line Results from CTH-105 Phase 2 Study of APL-130277 for the Treatment of OFF Episodes in Patients with Parkinson's Disease**

*Clinically meaningful improvement in motor control occurred in as early as 10 minutes after administration of APL-130277 and lasted longer than 90 minutes*

*Conference call begins at 8:00 a.m. Eastern time today*

**TORONTO (November 19, 2014) – Cynapsus Therapeutics Inc. (CTH: TSX-V) (CYNAF: OTCQX)**, a specialty pharmaceutical company focused on Parkinson's disease, today announced positive top-line results from its CTH-105 Phase 2 clinical trial of APL-130277 for the management of OFF motor symptoms of Parkinson's disease.

APL-130277 is the Company's fast-acting, sublingual, thin filmstrip formulation of apomorphine. OFF episodes are a complication of Parkinson's disease that leave patients rigid and unable to move and communicate. An estimated one quarter to one half of all people with Parkinson's disease whose symptoms are otherwise managed with ongoing drug therapy, experience OFF episodes at least once daily and up to six times daily, with each episode lasting between 30 and 120 minutes.

Highlights of the CTH-105 study results include:

- Out of 16 patients treated with APL-130277, 14 converted from OFF to ON, suggesting that APL-130277 may effectively manage OFF episodes in patients with Parkinson's disease
- Preliminary data show that several subjects converted to ON with the 10mg low dose, and 14 of 16 subjects converted ON with all available doses (i.e. 10, 15, 20, 25 and 30mg)
- Clinically meaningful improvement in motor control occurred in as early as 10 minutes after administration of APL-130277 and lasted longer than 90 minutes
- The maximum mean change from baseline UPDRS III was 18.4, which is a large clinically important difference
- APL-130277 treatment was safe and well tolerated, with no local irritation, no postural hypotension and a low number of nausea events

"The purpose of the CTH-105 study was to better understand the APL-130277 dose range that produced efficacy as measured by the change in the Unified Parkinson's Disease Rating Scale (UPDRS) part III, a scale used by neurologists to measure the severity of Parkinson's disease OFF and motor symptoms, compared with baseline. We are encouraged that APL-130277 provided clinical benefit at all five doses used in this study," said Dr. Albert Agro, Chief Medical Officer of Cynapsus. "These preliminary data show that APL-130277 was able to convert patients from a severe OFF state in the morning to ON. In addition, treatment was associated with a 45% improvement in motor function based on the change in UPDRS part III from baseline. The mean dose needed to terminate the OFF episode was 18.4mg. In addition, those patients achieving a response at higher doses appeared to adapt to the treatment, as seen by the lack of nausea at higher doses."

## Phase 2 Study Design

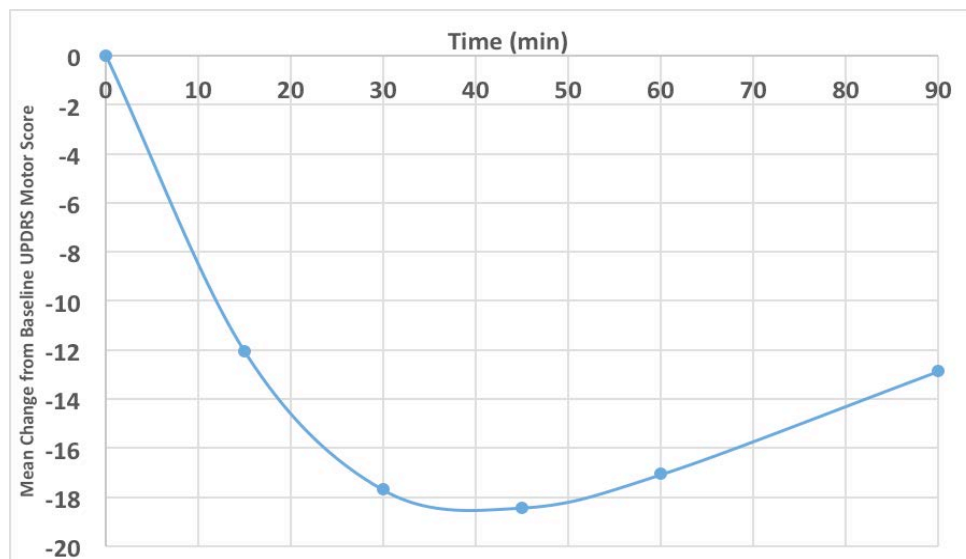
In the CTH-105 multicenter open-label study, APL-130277 was assessed in 16 patients with Parkinson's disease who experience the debilitating effects of OFF episodes, with a total duration of OFF of at least two hours daily. To date, 16 patients have completed the dosing regimen, which was the planned sample size for the study. Due to over enrollment, an additional three patients are still in dosing. OFF episodes were achieved by having patients take their last dose of levodopa the night before they came into the clinic. Patients were not allowed to take their first dose of levodopa in the morning, resulting in a severe OFF state that is one of the most difficult to convert and maintain in an ON state. Patients were then given escalating doses of APL-130277 (at a minimum of three hours between doses) until ON was achieved, as documented by study staff, the patient, and a clinician assessment of UPDRS part III. The UPDRS III part score was measured at 15, 30, 45, 60 and 90 minutes.

## Phase 2 Study Results

All five doses of APL-130277 used in the study (10, 15, 20, 25 and 30mg) resulted in patients moving from OFF to ON. The mean baseline UPDRS part III in an OFF state was 41.4, and the maximum mean change from baseline UPDRS part III was 18.4. The mean dose required to convert patients to ON was 18.4mg. The onset of a clinically meaningful improvement was seen in as early as 10 minutes and lasted up to 90 minutes, the last time point measured in this study. The mean time to ON as reported by study staff was 22 minutes. Cynapsus believes that these data strongly support the conclusion that APL-130277 is associated with the robust and rapid management of OFF episodes.

The graph below shows the mean change from baseline in UPDRS part III for the 14 subjects who converted to ON. Two patients dosed at the highest available dose (30mg) did not achieve a full ON as assessed by the investigator, suggesting that higher doses may be required for some patients.

**Mean Change in UPDRS Part III from Baseline Over Study Period  
for Patients Converting from OFF to ON**



Treatment with APL-130277 was safe and well tolerated. Nausea was reported by three subjects at doses of 10, 15 and 20mg. One of these patients also experienced a mild episode of emesis. There were no

reports of nausea at higher doses. There were no reports of local irritation or hypotension in any subject treated. A total of 60 doses of APL-130277 were administered to the 16 patients who completed dosing in the CTH-105 study.

Based on the findings of this study, Cynapsus is planning to conduct pivotal studies of longer duration and with larger patient numbers to confirm these results. These pivotal studies are expected to form the registration package necessary for a 505(b)(2) New Drug Application with the U.S. Food and Drug Administration expected to be submitted in 2016.

“The results of this Phase 2 trial are important as the data show that APL-130277 provided Parkinson’s patients with a rapid improvement in motor function during OFF episodes,” said Anthony Giovinazzo, President and CEO of Cynapsus. “APL-130277 is being developed to address a significant unmet need facing people with Parkinson’s disease today. The CTH-105 trial results lead us to maintain that APL-130277 may be able to serve the majority of Parkinson’s patients seeking to restore movement rapidly, on demand, with an easy to retrieve and to administer form of apomorphine, the only approved and most efficacious drug for this purpose.”

“OFF episodes are debilitating events for people with Parkinson’s disease. A recent survey by The Michael J. Fox Foundation of 3,000 Parkinson’s patients revealed that nearly half said their OFF time was moderate or severe, causing them to avoid or stop activities,” said Dr. Todd Sherer, CEO of The Michael J. Fox Foundation for Parkinson’s Research, which provided \$500,000 in funding for this study. “A rapid and reliable therapy that can address OFF episodes would be a major advancement in treatment. These results suggest that APL-130277 could provide patients with improved quality of life, and as supporters of this program from its early days, we look forward to continued success in Phase 3 trials.”

### **About Parkinson’s Disease and OFF Episodes**

More than 1 million people in the U.S. and an estimated 4 to 6 million people globally suffer from Parkinson’s disease. Parkinson’s disease is a chronic and progressive neurodegenerative disease that impacts motor activity, and its prevalence is increasing with the aging of the population. OFF episodes are a complication of Parkinson’s disease that leave patients rigid and unable to move and communicate. An estimated one quarter to one half of all people with Parkinson’s disease whose symptoms are otherwise managed with ongoing drug therapy experience OFF episodes at least once daily and up to six times daily, with each episode lasting between 30 and 120 minutes.

OFF and motor symptoms of Parkinson’s disease are measured by UPDRS part III. The UPDRS is used by neurologists to measure the severity of Parkinson’s disease.

### **About Apomorphine**

Apomorphine is the only drug that can rapidly convert a patient from OFF (unable to move) to ON (fully functional). Unfortunately for Parkinson’s patients, apomorphine is currently only available only as an injection, which can be painful and difficult to administer, particularly while suffering an OFF episode.

Cynapsus’ APL-130277 drug candidate is the only oral formulation of apomorphine for the treatment of OFF episodes. APL-130277 is a strip that a Parkinson’s patient can place under his or her tongue when an OFF episode is starting. If approved, APL-130277 will provide patients with a convenient and easy alternative to multiple daily injections.

## Conference Call and Webcast

Cynapsus management will host a conference call with accompanying slides to discuss these findings and answer questions today at 8:00 a.m. Eastern time. Shareholders and other interested parties can participate in the call by dialing 888-883-4599 (domestic) or 484-653-6821 (international) and referencing conference ID number 37666252. The call and slides will also be webcast live on the Company's website at [www.cynapsus.ca](http://www.cynapsus.ca) on the Calendar and Alerts page under Investor Relations.

A replay of the conference call will be accessible beginning two hours after its completion through November 26, 2014 by dialing 855-859-2056 (domestic) or 404-537-3406 (international) and referencing conference ID number 37666252. The call and slides will also be archived for 90 days on the Company's website at [www.cynapsus.ca](http://www.cynapsus.ca) on the Calendar and Alerts page under Investor Relations.

## About Cynapsus Therapeutics

Cynapsus is a specialty pharmaceutical company developing a sublingual thin filmstrip for the acute rescue of OFF motor symptoms of Parkinson's disease. Cynapsus' drug candidate, APL-130277, is an easy-to-use, fast-acting formulation of apomorphine, which is the only approved drug (in the United States, Europe, Japan and other countries) to rescue patients from OFF episodes. Cynapsus is focused on maximizing the value of APL-130277 by completing pivotal studies in advance of a 505(b)(2) New Drug Application (NDA) expected to be submitted in 2016.

More information about Cynapsus is available at [www.cynapsus.ca](http://www.cynapsus.ca) and at the System for Electronic Document Analysis and Retrieval (SEDAR) at [www.sedar.com](http://www.sedar.com).

## Contact Information

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## Forward Looking Statements

This announcement contains "forward-looking statements" within the meaning of applicable securities laws. Generally, these forward-looking statements can be identified by the use of forward-looking terminology such as "plans", "expects" or "does not expect", "is expected", "budget", "scheduled", "estimates", "forecasts", "intends", "anticipates" or "does not anticipate", or "believes" or variations of such words and phrases or state that certain actions, events or results "may", "could", "would", "might" or "will be taken", "occur" or "be achieved". Forward-looking statements are subject to known and unknown risks, uncertainties and other factors that may cause the actual results, level of activity, performance or achievements of Cynapsus to be materially different from those expressed or implied by such forward-looking statements, including but not limited to those risks and uncertainties relating to Cynapsus'

business disclosed under the heading “Risk Factors” in its March 26, 2014, Annual Information Form and its other filings with the various Canadian securities regulators which are available online at [www.sedar.com](http://www.sedar.com). Although Cynapsus has attempted to identify important factors that could cause actual results to differ materially from those contained in forward-looking statements, there may be other factors that cause results not to be as anticipated, estimated or intended. There can be no assurance that such statements will prove to be accurate, as actual results and future events could differ materially from those anticipated in such statements. Accordingly, readers should not place undue reliance on forward-looking statements. Cynapsus does not undertake to update any forward-looking statements, except in accordance with applicable securities laws.

Neither the TSX Venture Exchange nor the OTCQX International has approved or disapproved of the contents of this press release.

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