Apomorphine sublingual film for OFF episodes in Parkinson's disease

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Expert faculty

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Disclosures

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Dr. Comella is a paid consultant for Sunovion Pharmaceuticals Inc. She also serves on the editorial board of Clinical Neuropharmacology and Sleep Medicine. She has received compensation/honoraria for services as a consultant or an advisory committee member from: Acadia Pharmaceuticals; Acorda Therapeutics; AEON Biopharma; Allergan, Inc; Ipsen Pharmaceuticals; Jazz Pharmaceuticals; Lundbeck Ltd; Merz Pharmaceuticals; Neurocrine Biosciences Inc; Revance Therapeutics Inc. She also receives royalties from Cambridge University Press and Wolters Kluwer.

Disclosures

Robert Hauser

Dr. Hauser is a paid consultant for Sunovion Pharmaceuticals Inc. He has also acted as a consultant for Acadia Pharmaceuticals, Acorda Therapeutics, Adamas Pharmaceuticals, Affiris, AlphaSights, Amneal Pharmaceuticals, ApoPharma, Aptinyx, Aranca, Axovant, Britannia, Cadent, CAVR, Cerevel Therapeutics, ClearView Healthcare Partners, Clinical Score LLC, CNS Ratings LLC, Compass Group, Curium Pharma, Decision Resource Group (DRG), Dedham Group, Defined Health, Denali, Enterin, Extera Partners, F. Hoffmann-La Roche Ltd., First Word, Gerson Lehman Group (GLG), Global Kinetics Consulting (GKC), Global Life Sciences, Guidepoint Global, Huron, Impax Laboratories, Impel Neuropharma, Inhibikase, InSearch Consulting, Insignia Strategies, In-Trace Medical Systems, ISCO, IQVIA, Jazz Pharmaceuticals, Kaiser Permanente, Kashiv Pharma, KeiferRX LLC, KeyQuest, KX Advisors, Kyowa Kirin Pharmaceuticals, L.E.K Consulting, LifeSciences Consultants, Lundbeck A/S, Medscape, MJFF, MPTA, Neuro Challenge Foundation for PD, Neurocrine Biosciences, NeuroDerm, NOVUS, Orion, Parkinson Study Group, Pennside Partners, Perception OpCo, Pharmather, PSL Group, Regenera Pharma, Research Catalyst, Revance Therapeutics, Schlesinger Associates, Scion NeuroStim LLC, Seelos Therapeutics, Slingshot Insights, Sunovion Pharmaceuticals, Supernus Pharma, Teva Pharmaceuticals, Tolmar Inc, and US World Meds. He has also received research support from AbbVie, Axovant Sciences Ltd, Biogen Inc, Biotie Therapies Inc, Cavion, Inc, Centogene, Cerevance, Cerevel Therapeutics Inc, Civitas Therapeutics Inc, Cynapsus Therapeutics, Enterin Inc, F. Hoffman-La Roche Ltd, Global Kinetics Corporation (GKC), Impax Laboratories, Intec Pharma, Jazz Pharmaceuticals, Michael J Fox Foundation, Neuraly, NeuroDerm Ltd, Northwestern University, Pfizer, Pharma Two B, Revance Therapeutics, Sanofi US Services Inc, and Sun Pharma Advanced Research Company.

Dr. Hauser has participated in Scientific Advisory Boards or Panels for Inhibikase, Impel Neuro Pharma, and Cerespir, as well as Speaker Bureau activities for Acorda Therapeutics, Adamas Pharmaceuticals, Amneal Pharmaceuticals, Kyowa Kirin Pharmaceuticals, Neurocrine Biosciences, Sunovion Pharmaceuticals, and US World Meds. He holds stocks or shares in Inhibkase and Axial Therapeutics, and receives royalties/holds patents relating to the USF PD Diary.

Agenda

- An acute, intermittent treatment for OFF episodes in people with Parkinson’s disease
- Self-administration of APL for OFF episodes in people with Parkinson’s disease
- Select safety considerations when treating patients with APL

An acute, intermittent treatment for OFF episodes in people with Parkinson's disease

OFF episodes in patients with Parkinson's disease

- In patients with PD, an OFF episode typically refers to the recurrence of motor symptoms while receiving chronic levodopa-based therapy[1]
- During OFF episodes, the motor symptoms are usually characteristic of PD (e.g., recurrent tremor, walking/balance impairment, slowness of movement)[1]
- In addition to motor symptoms, OFF episodes can also be associated with the recurrence of non-motor PD symptoms, such as anxiety, dysphagia, fatigue, dizziness and depression[2]

PD, Parkinson's disease.

1. Chou K. The spectrum of OFF in Parkinson's disease: What have we learned over 40 years? Park Rel Disord. 2018;51:9-16.
2. Storch A, Schneider CB, Wolz M, et al. Nonmotor fluctuations in Parkinson disease: severity and correlation with motor complications. Neurology. 2013;80:800–9.

Studies of APL for the treatment of OFF episodes in patients with PD

CTH-300[1]

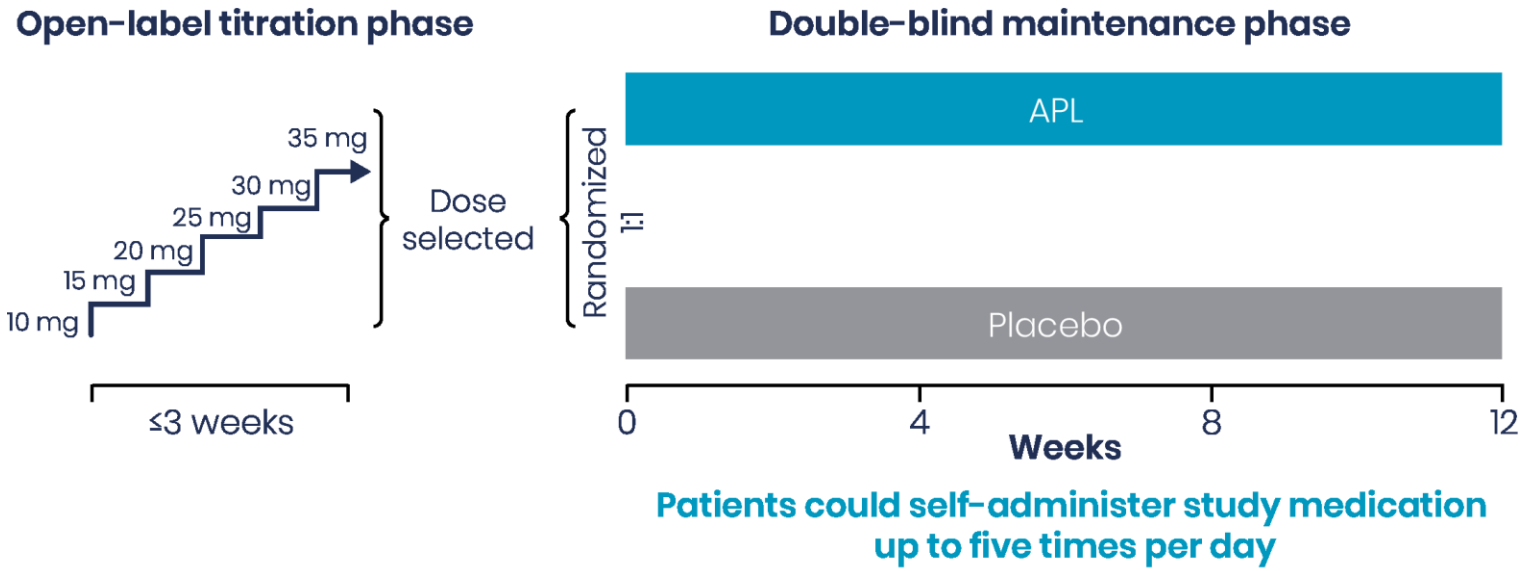
12-week, randomized, double-blind, placebo-controlled study of APL for the acute treatment of OFF episodes in patients with PD

CTH-301[2]

Ongoing, 48-week, open-label study of APL for the acute treatment of OFF episodes in patients with PD

1. Olanow CW, et al. Efficacy, safety and tolerability study of APL-130277 for the acute treatment of OFF episodes in patients with Parkinson's disease. Lancet Neurol. 2020;19:135-144 [NCT024609090];
2. NIH US National Library of Medicine. Clinicaltrials.gov: Open-label phase 3 study to examine the long-term safety, tolerability, and efficacy of APL-130277 for the acute treatment of OFF episodes in patients with Parkinson's disease. Available from: https://www.Clinicaltrials.gov/ct2/show/NCT02542696.

CTH-300 study design*



*Clinicatrials.gov identifier: NCT02469090
Antiemetic medication (trimethobenzamide 300 mg TID [US] or domperidone 10 mg BID [OUS]) was required per protocol for 3 days prior to titration; medication could be discontinued during the double-blind maintenance phase at the Investigator's discretion.

BID, twice daily; OUS, outside of the United States; TID, three times a day; US, United States
Olanow CW, et al. Lancet Neurol. 2020; 19(2): 135-144.

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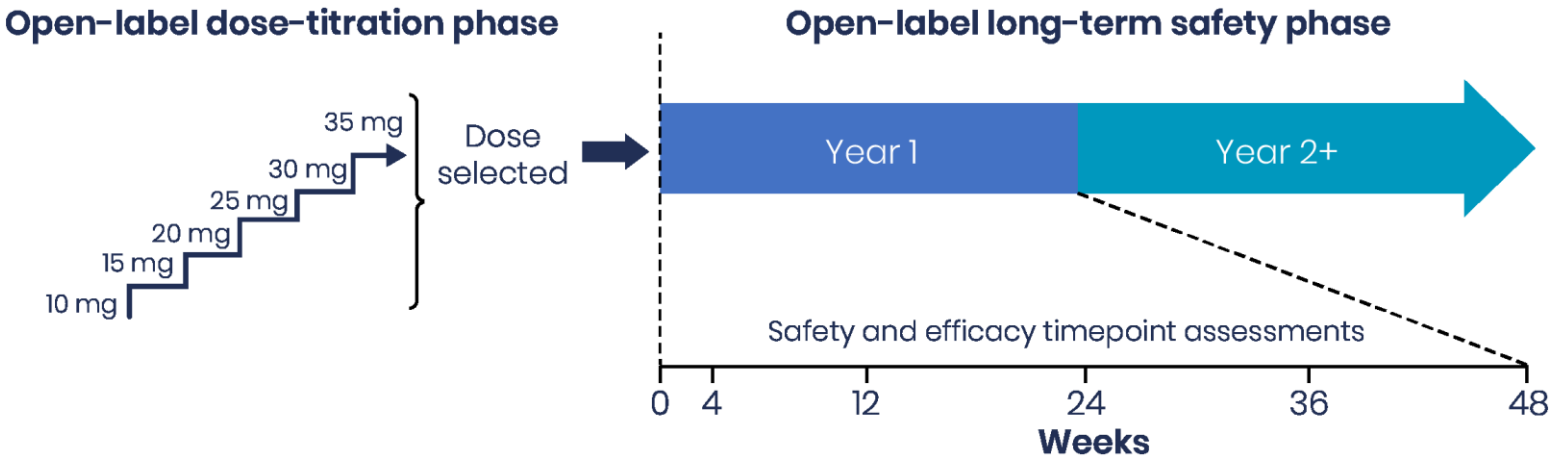
CTH-301 study design*



During the long-term safety phase, patients self-administered their titrated dose of APL at home for up to five OFF episodes per day with a minimum of 2 hours between doses; doses could be adjusted at the Investigator's discretion for safety or lack of efficacy

*Clinicatrials.gov identifier: NCT02542696
Antiemetic medication (trimethobenzamide 300 mg TID [US] or domperidone 10 mg BID [OUS]) during the dose titration phase was initially mandatory and was subsequently made optional (at the Investigator's discretion if clinically warranted) after protocol amendment 4.

Factor S, et al. Presented at: International Parkinson and Movement Disorder Society (MDS) Virtual Congress 2020; September 12-16, 2020. Abstract 88.

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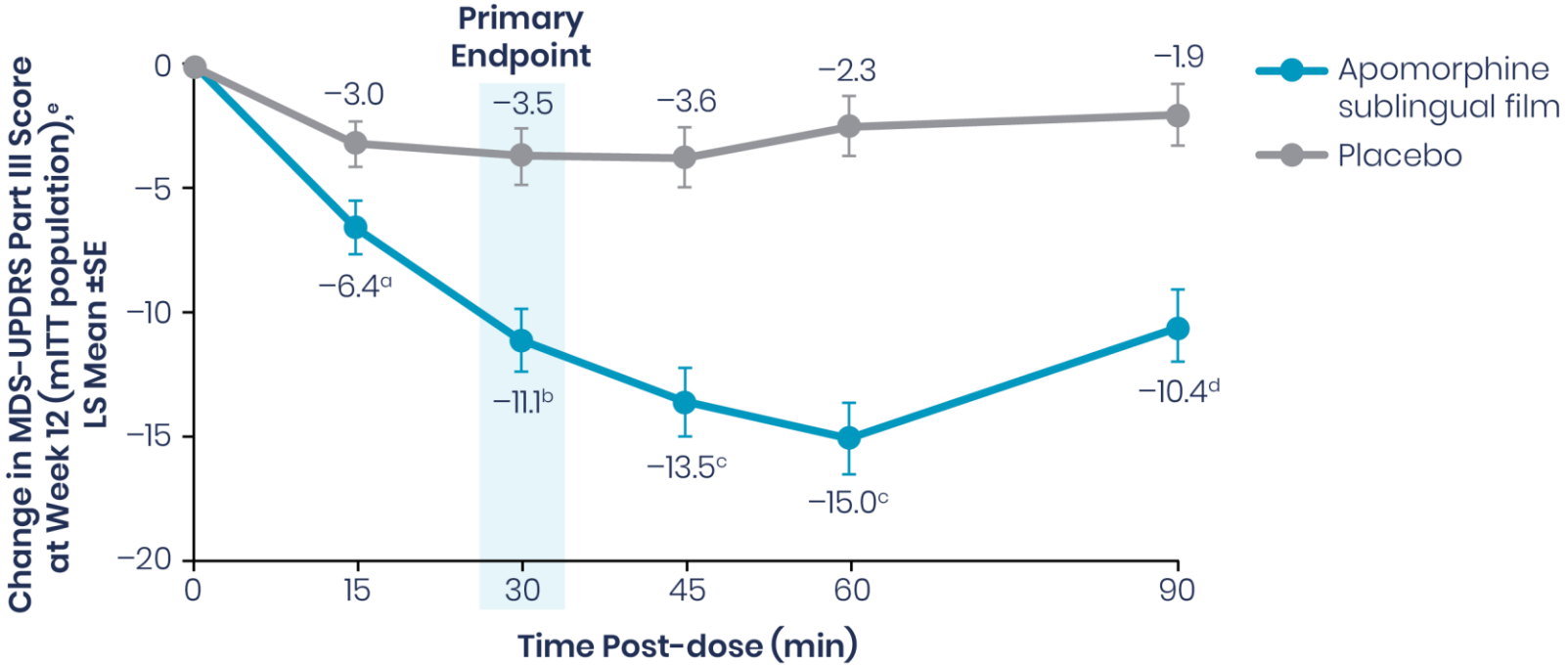
Change from pre-dose to 30 minutes post-dose in MDS-UPDRS part III score at Week 12 (CTH-300)



[a]P=0.039. [b]P=0.0002. [c]P<0.0001. [d]P=0.0003. [e]mITT population included all patients who were dosed with apomorphine sublingual film in the double-blind maintenance phase.
mITT, modified intention-to-treat; LS, least squares; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; SE, standard error.
Olanow CW, et al. Lancet Neurol. 2020; 19(2): 135-144.

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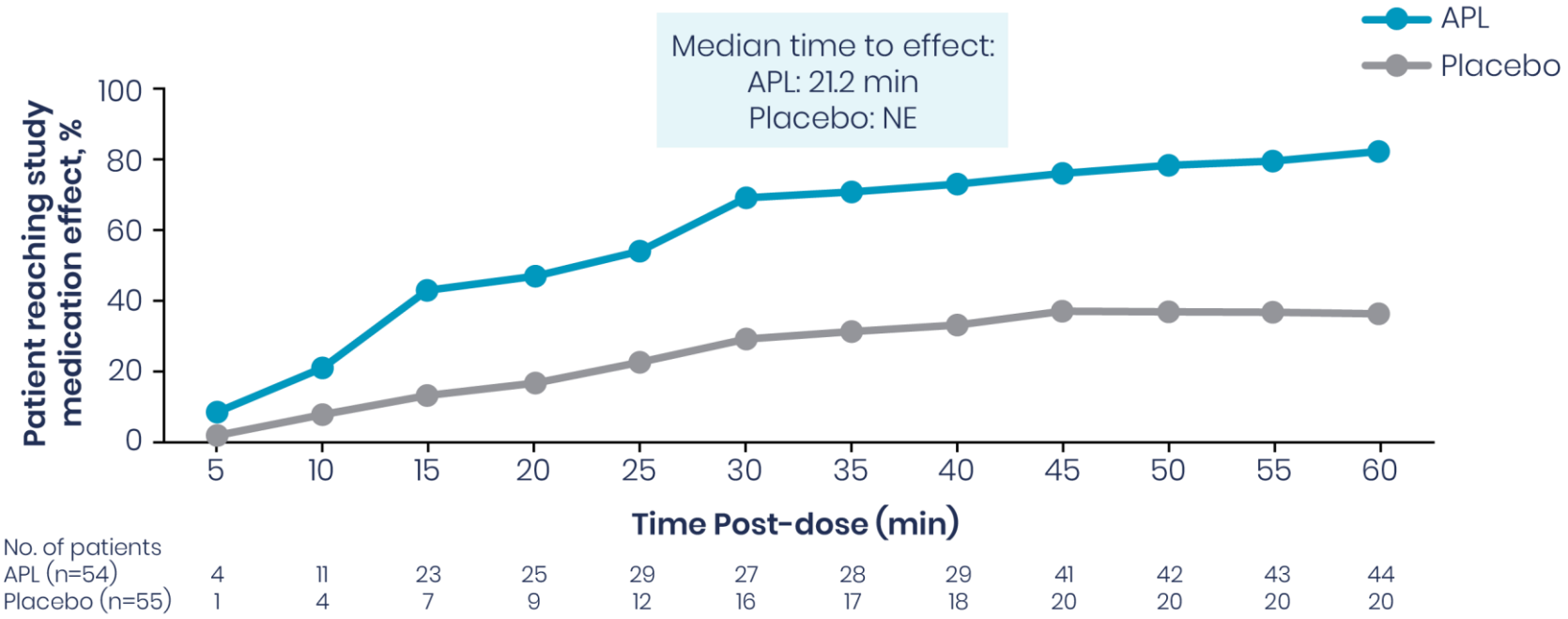
Time to onset of study medication effect at Week 12 (CTH-300; mITT population)[a,1,2]

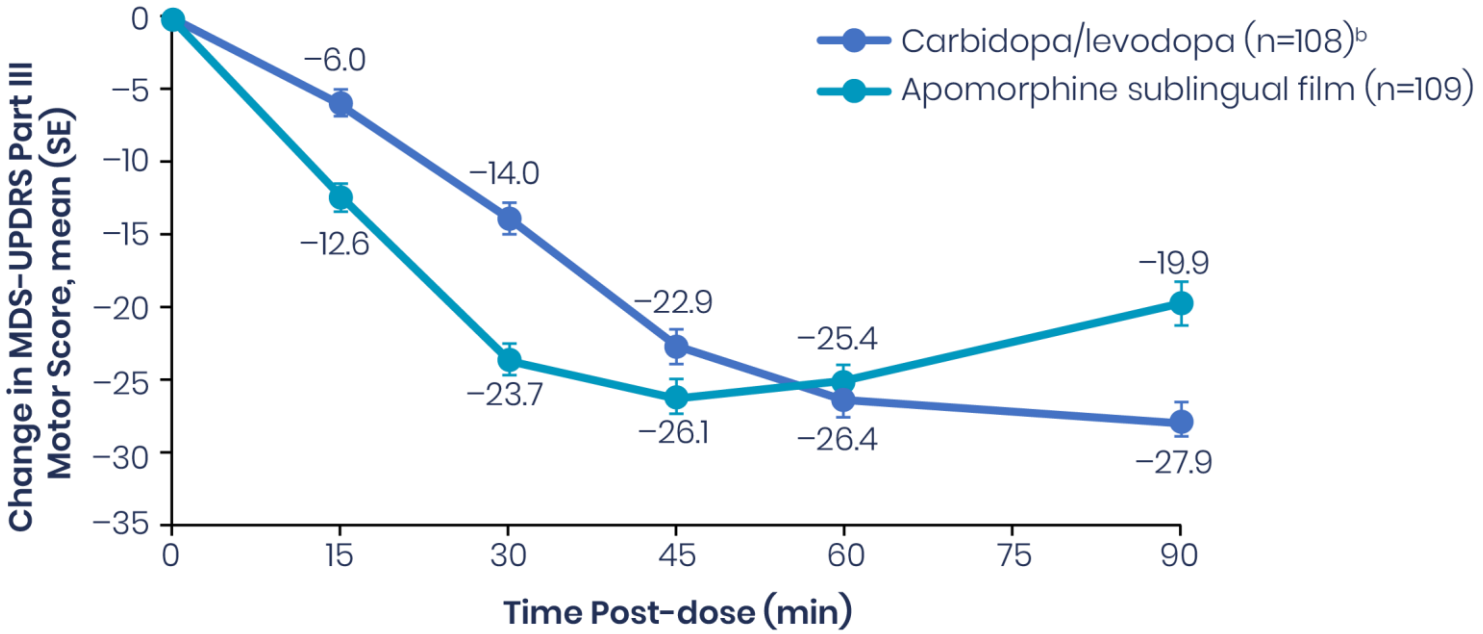


[a]Each endpoint was tested sequentially in the hierarchy. Once a *P* value was >0.05, all subsequent analyses were no longer considered statistically significant. Following the 3rd endpoint, the remaining results are presented with nominal *P* values for descriptive purposes. The endpoint above was endpoint #10.

NE, not evaluable.

1. Factor SA, et al. Presented at the International Congress of Parkinson's Disease and Movement Disorders; October 5-9, 2018; Hong Kong. Poster 247; 2. Olanow CW, et al. Lancet Neurol. 2020; 19(2): 135-144.

Change from pre-dose in MDS-UPDRS part III score for APL and carbidopa/levodopa (CTH-300 *post hoc* analysis)[a]



Study limitations: (1) While APL was titrated to tolerance and effect, levodopa was administered at the patient's usual morning dosage and may not have been optimally dosed; (2) CTH-300 was not designed to evaluate the safety of APL compared with levodopa. APL was titrated to a level (10–35 mg) that provided a FULL ON (n = 109). MDS-UPDRS Part III score was assessed pre-dose and at 15, 30, 45, 60, and 90 min post-dose.

[a]At Screening - all patients were on stable doses of carbidopa/levodopa and the dose of carbidopa/levodopa administered at screening was the first dose of patients' normal daily maintenance therapy; the dose of carbidopa/levodopa was not titrated during screening.
[b]Carbidopa/levodopa data were missing for 1 patient.

Hui JS, et al. Parkinsonism Relat Disord 2020;79:110–116.

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Self-administration of APL for OFF episodes in people with Parkinson's disease

Home diaries in CTH-300 captured patient-reported motor status 30 minutes post-dose

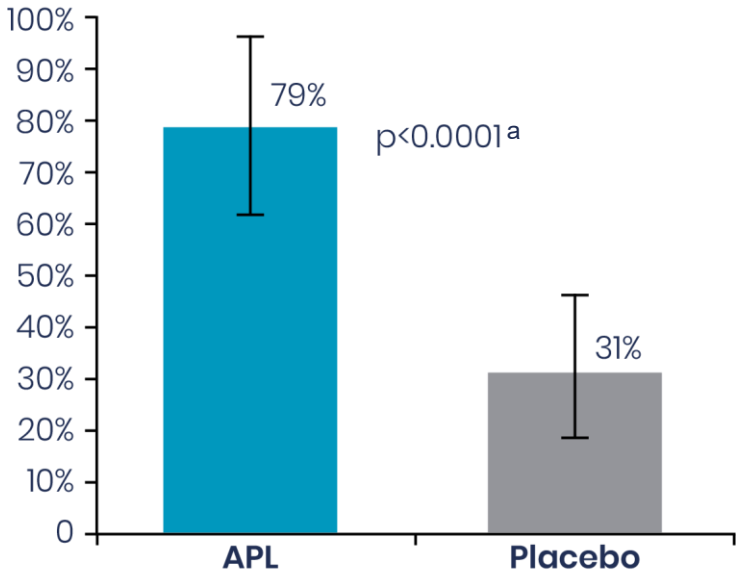
Methods

- Home diaries were completed by patients during the two days prior to each study maintenance visit

Results

- APL provided a full ON response after 30 mins more frequently than placebo (Figure 1)
- *Post hoc* analysis of home diaries data showed that the effectiveness of APL was independent of the time of administration and dose

Figure 1. Percentage of treated OFF episodes during the 2 days prior to the Week 12 visit with full ON at 30 minutes post-dose, LS Mean (95% CI)



Study limitations: (1) Accuracy of patient data reporting (2) Missing data (3) Limitations related to correct administration technique (4) Diaries completed only during the 2 days prior to each maintenance visit.
[a]Endpoints were tested in a prespecified hierarchical order. This nominal p-value is shown for descriptive purposes without adjustment for multiplicity.
CI, confidence interval; LS, least squares.
Hauser RA, Mehta SH, Blum D, et al. Patient-reported motor responses to apomorphine sublingual film on home dosing and response diaries. Abstract 141; presented at 3rd Pan American Parkinson's Disease and Movement Disorders Congress (MDS-PAS), February 14–16, 2020; Miami, Florida, United States.

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Adverse events seen with the use of APL in CTH-300

- Most common adverse reactions (incidence ≥10% in patients treated with APL and greater than placebo) were:

  - Nausea
  - Oral/pharyngeal soft tissue swelling
  - Oral/pharyngeal soft tissue pain and parasthesia
  - Dizziness
  - Somnolence

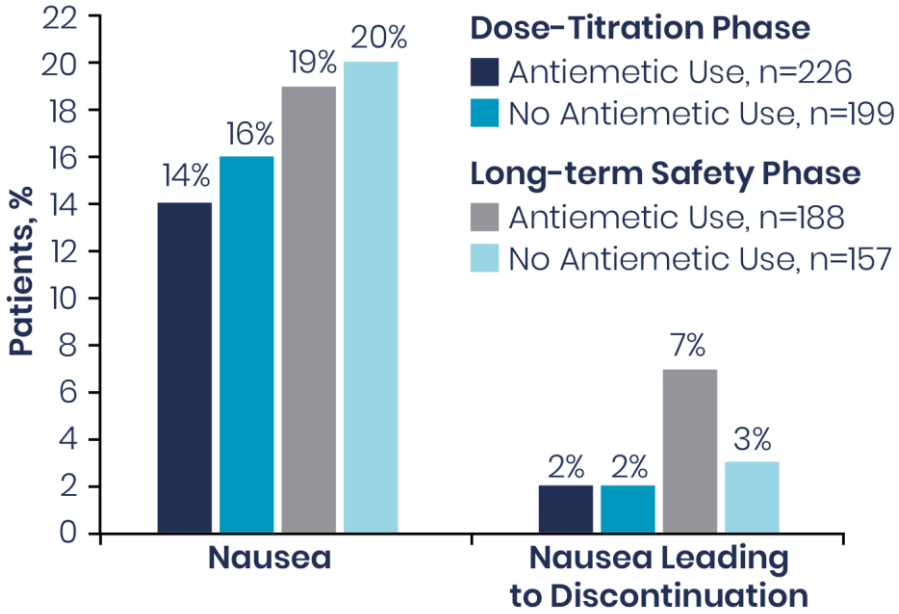
Select safety considerations when treating patients with APL

Rates of nausea with APL during dose titration in CTH-301

CTH-301: interim *ad hoc* analysis of the dose titration phase

- Incidence of nausea / nausea resulting in discontinuation was similar regardless of antiemetic use

Nausea by antiemetic use – interim *ad hoc* analysis of a May 2019 data cut



Ellenbogen AL, Nicholas AP, Hauser RA, et al. Apomorphine sublingual film for the treatment of "OFF" episodes in patients with Parkinson's disease: impact of concomitant antiemetics and dopamine agonists on nausea and vomiting. Presented at the International Parkinson and Movement Disorder Society (MDS) Virtual Congress, September 12–16, 2020. Abstract 883.

Impact of APL on dyskinesia rates

- In both the CTH-300 and CTH-301 studies, little to no impact of APL on dyskinesia was observed

CTH-300

TEAEs of dyskinesia were infrequent during maintenance treatment phase

(0% with APL *vs* 2% with placebo)

CTH-301 interim analysis[a]

TEAEs of dyskinesia occurred in 6% of patients receiving APL, independent of dose (10–35 mg)

[a]May 2019 data cut.
TEAE, treatment-emergent adverse event.
Klos KJ, Hui JS, Robottom BJ, et al. Apomorphine sublingual film for the treatment of "OFF" episodes in patients with Parkinson's disease: impact on dyskinesia. Presented at the International Parkinson and Movement Disorder Society (MDS) Virtual Congress, September 12–16, 2020.

Impact of APL on impulse control or compulsive behaviours

- In both the CTH-300 and CTH-301 studies, APL was associated with little to no impact on impulse control disorders[a]

CTH-300

QUIP-RS score (Week 12):

-0.8 with APL *vs* -2.8 with placebo

CTH-301 interim analysis[b]

A mean change from baseline of +0.3 in **QUIP-RS score (Week 48)** (n=30)

[a]as measured by QUIP-RS.
[b]May 2019 data cut.
ICD, impulse control disorder; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale.
Espay AJ, et al. Apomorphine sublingual film for the treatment of "OFF" episodes in patients with Parkinson's disease: impact on impulse control disorders. Presented at the International Parkinson and Movement Disorder Society (MDS) Virtual Congress, September 12–16, 2020.

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