Apomorphine sublingual film for OFF episodes in Parkinson's disease

An expert panel discussion recorded in March 2021

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Expert panel

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Disclosures

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Agenda

- What are OFF episodes in Parkinson's disease? How do they occur and how are they treated?
- What were the results of the randomized phase of the pivotal study (CTH-300) of APL for the treatment of OFF episodes in Parkinson's disease?
- What were the results of the open-label, dose-titration phase of the pivotal study (CTH-300) of APL for the treatment of OFF episodes in Parkinson's disease?
- How will the results of the pivotal study of APL (CTH-300) change the way you treat OFF episodes in patients with Parkinson's disease?

APL, apomorphine sublingual film.

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What are OFF episodes in Parkinson's disease? How do they occur and how are they treated?

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]

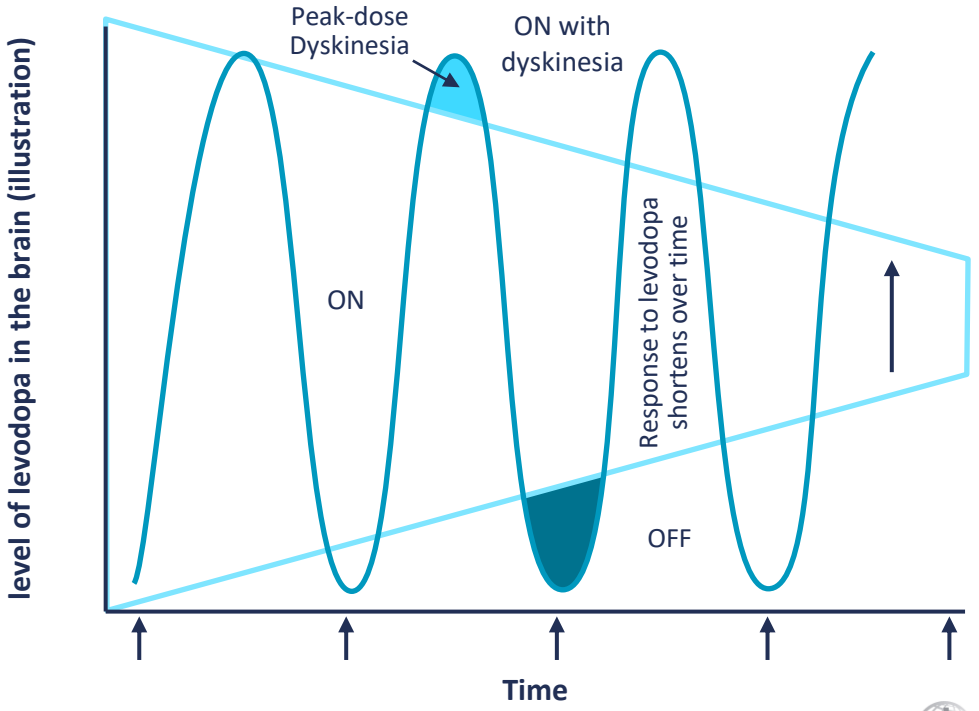
PD, Parkinson's disease.

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.

Why do OFFs occur?

As disease progresses, there are fewer healthy neurons to release their own dopamine, or to convert levodopa to dopamine and release it properly. This, coupled with the short half-life of levodopa, causes pulsatile stimulation of postsynaptic receptors and dopamine release

Therapeutic window of levodopa changes over time



Adapted from Living Medical eTextbook: Neurology—Parkinson's Disease Edition: Early Diagnosis and Comprehensive Management, Chapter 5. Hauser RA, editor. .

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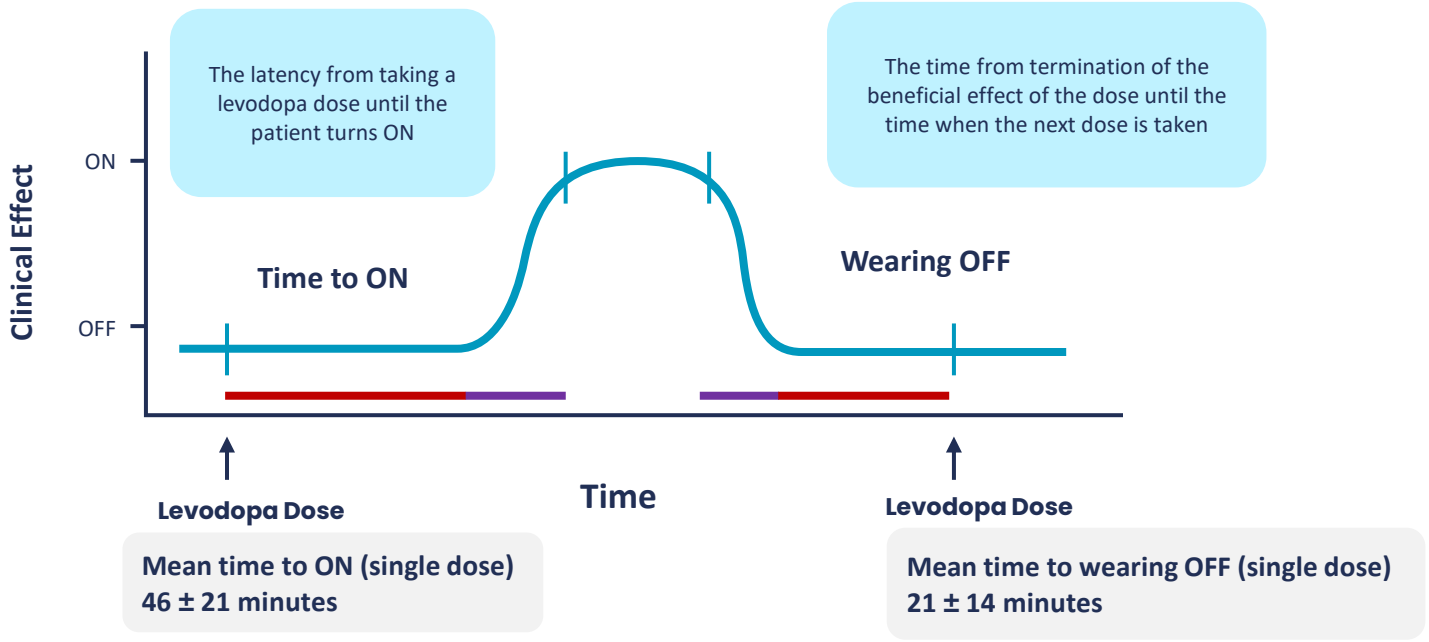
The spectrum of OFF episodes – delayed ON, levodopa dose failure and wearing OFF between doses



Based on a study of 20 patients with advanced PD receiving levodopa (mean total daily dose of 821 mg, in 5–9 divided daily doses).
Adapted from Merims D, et al. Clin Neuropharmacol. 2003;26:196–198.

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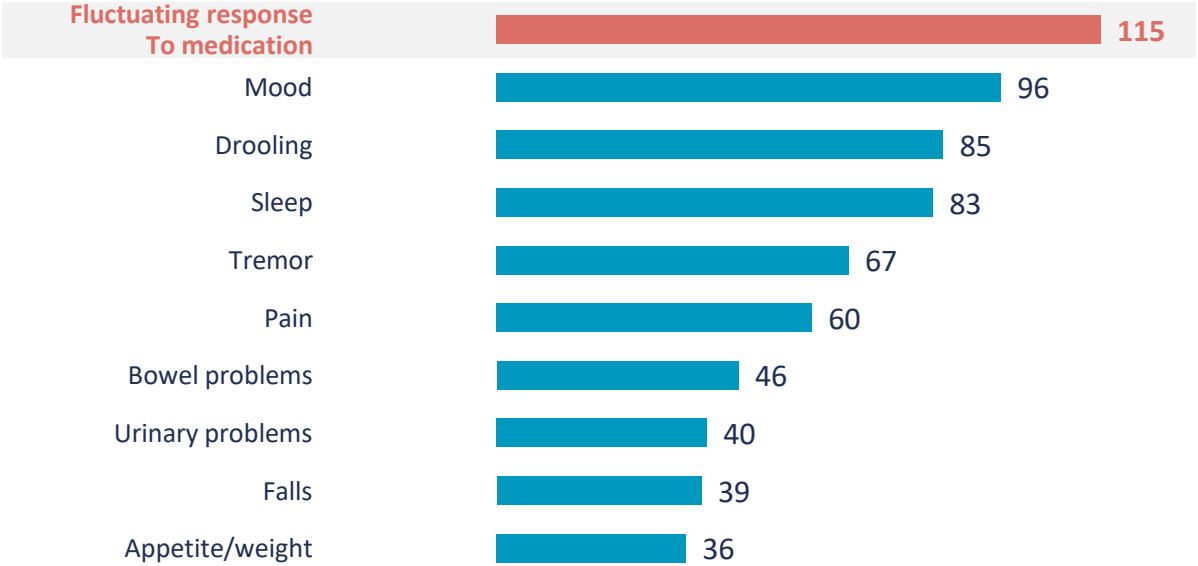
Fluctuating response to medication is the most bothersome complaint from the patient perspective[a]



[a]Responses from 173 patients with ≥6 years of disease duration were weighted according to their ranking and the weighted sum of each symptom was accrued.
Politis M, et al. Mov Disord. 2010;25:1646–1651.

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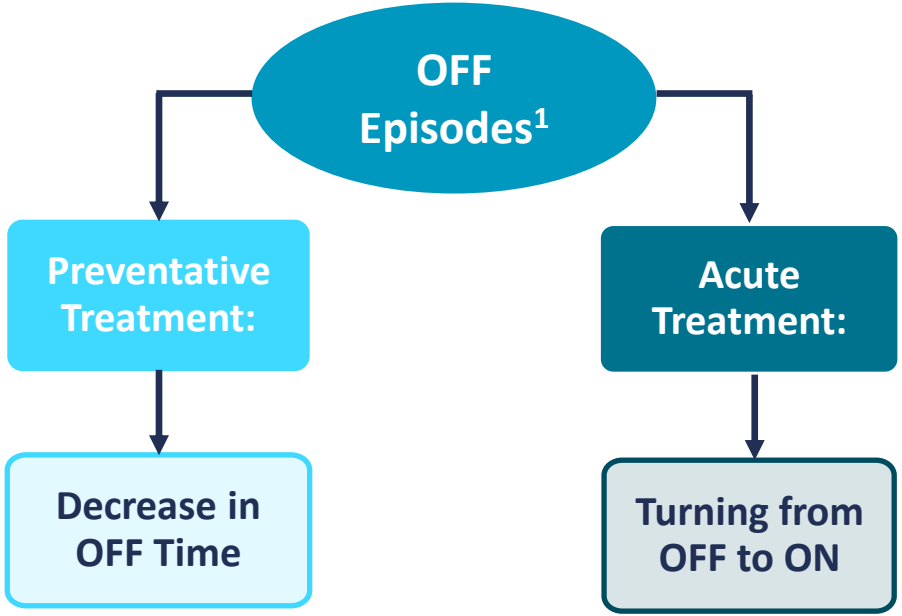
Treatment approaches for OFF episodes

- Various pharmacologic approaches are efficacious in reducing OFF time (on-extenders) for patients with PD[2,3]
- Despite these approaches, some patients still spend several hours per day in an OFF state[3,4]



1. Swope DM. Neurology. 2004;62(Suppl 4):S27–S31. 2. Fox SH, et al. Mov Disord. 2018;33:1248–1266. 3. Fabbri M, et al. Drugs Aging. 2018;35:1041–1054. 4. Antonini A, et al. Mov Disord. 2018; 33:900–908.

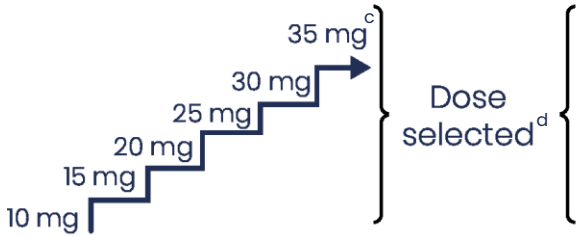
What were the results of the randomized phase of the pivotal study (CTH-300) of APL for the treatment of OFF episodes in Parkinson's disease?

CTH-300 study design*[1,2]

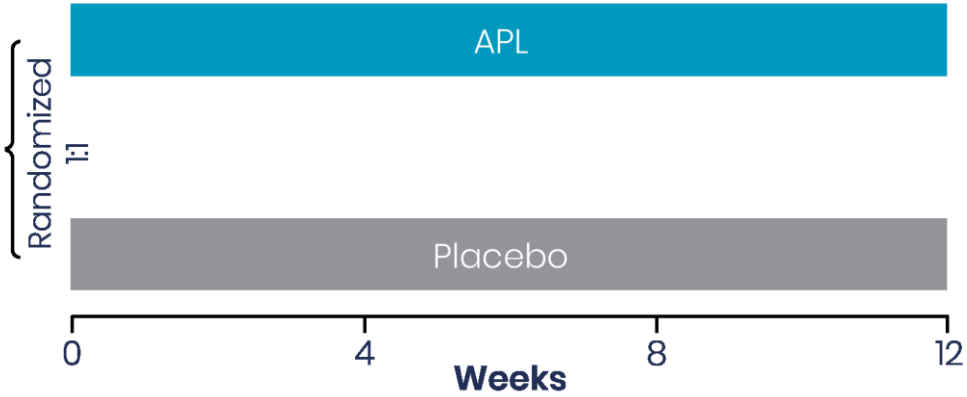
Screening phase office visits (Levodopa challenge)[a,b]

Informed consent

Open-label titration phase



Double-blind maintenance phase



Patients could self-administer study medication five times per day, with doses separated by at least 2 hours

Antiemetic medication (trimethobenzamide 300 mg TID [US] or domperidone 10 mg BID [OUS]) was initiated 3 days prior to the titration phase and could be discontinued during the double-blind maintenance phase at the Investigator's discretion

*Clinicatrials.gov identifier: NCT02469090
[a]Patient training of OFF vs ON occurred as part of the levodopa challenge during the screening phase; any patient who could not differentiate between these states was deemed a screen failure;
[b]Motor function was evaluated using MDS-UPDRS Part III, performed predose and at 15, 30, 45, 60, and 90 minutes postdose;
[c]The 35-mg dose (the highest dose studied) was given as 2 sublingual films consisting of 20 mg followed by 15 mg;
[d]The dose of apomorphine sublingual film during open-label titration that led to a FULL ON within 45 minutes without intolerable side effects was subsequently used during the randomized double-blind maintenance phase.
BID, 2 times a day; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; OUS, outside of United States; TID, 3 times a day.
1. Olanow CW et al. Lancet Neurol. 2020;19:135–144; 2. Hui JS, et al. Parkinsonism Relat Disord 2020;79:110–116.

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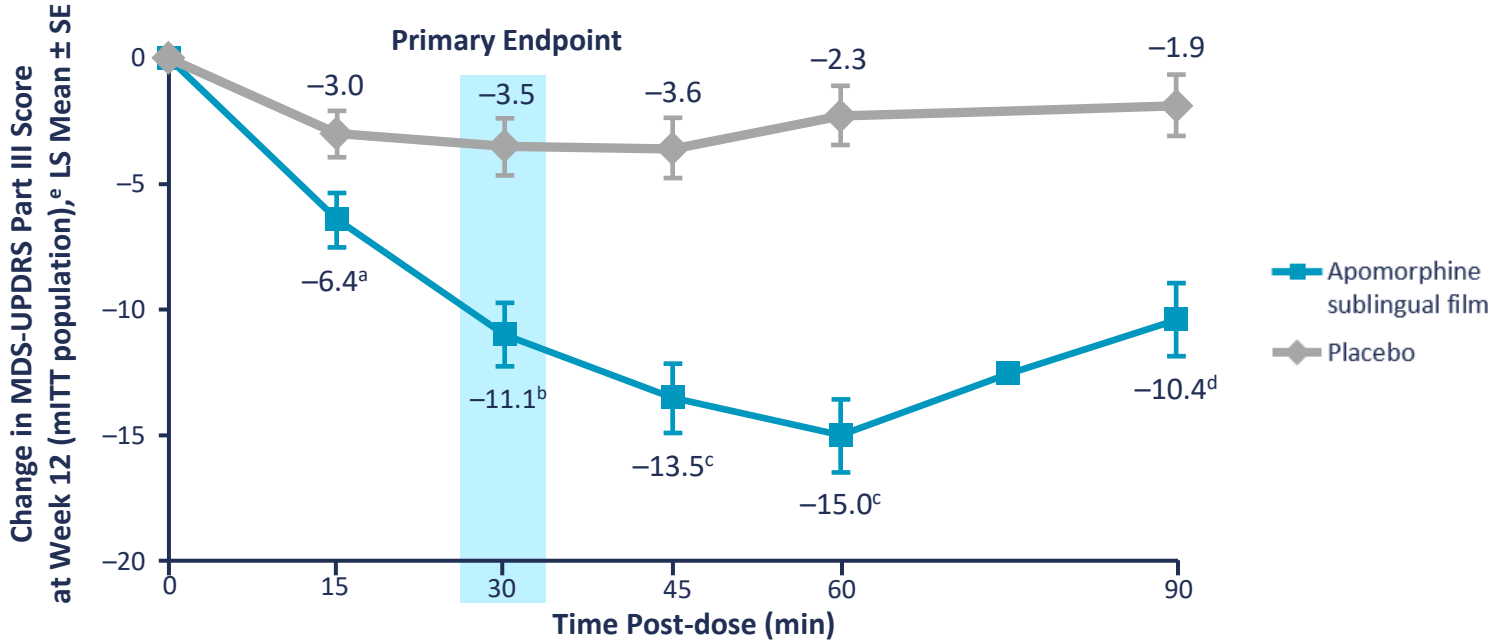
Baseline patient characteristics

Characteristic[a]	APL (n=54)	Placebo (n=55)
Age, y, mean (SD)	62.9 (9.79)	62.5 (8.12)
Men, n (%)	37 (69%)	31 (56%)
Women, n (%)	17 (31%)	24 (44%)
Race, n (%)		
White	50 (93%)	51 (93%)
Other	4 (7%)	4 (7%)
Time since PD diagnosis, y, mean (SD)	8.7 (4.25)	9.3 (3.84)
Time since motor fluctuations started, y, mean (SD)	4.7 (3.92)	4.5 (3.78)
OFF episodes per day, number, mean (SD)	3.9 (1.17)	3.8 (1.40)
MDS-UPDRS Part III (pre-dose), mean (SD)[b]	43.2 (15.17)	43.1 (14.38)
Total daily levodopa dose, mg, mean (SD)	1059 (563)	1008 (562)

Characteristic[a]	APL (n=54)	Placebo (n=55)
ON state modified Hoehn and Yahr score, n (%)		
1 or 1.5	0	1 (2%)
2 or 2.5	49 (91%)	42 (76%)
3	5 (9%)	11 (20%)
Missing	0	1 (2%)
Types of OFF episodes experienced, n (%)		
Morning akinesia	46 (85%)	44 (80%)
Wearing OFF	54 (100%)	54 (98%)
Delayed ON	29 (54%)	43 (78%)
Dose failure	22 (41%)	23 (42%)
Sudden OFF	26 (48%)	32 (58%)
Self-rated full ON response rate within 30 min post-dose, n (%)	37 (69%)	41 (75%)

[a]mITT population.
[b]Baseline score refers to the pre-dose MDS-UPDRS Part III motor examination score at the baseline visit (last titration visit at which the randomization dose was given).
mITT, modified intention-to-treat.
Olanow CW, et al. Lancet Neurol. 2020; 19: 135–144.

Change from Pre-dose to 30 Minutes Post-Dose in MDS-UPDRS Part III Score after 12 weeks (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.
LS, least squares; SE, standard error.
Olanow CW, et al. Lancet Neurol. 2020; 19: 135–144.

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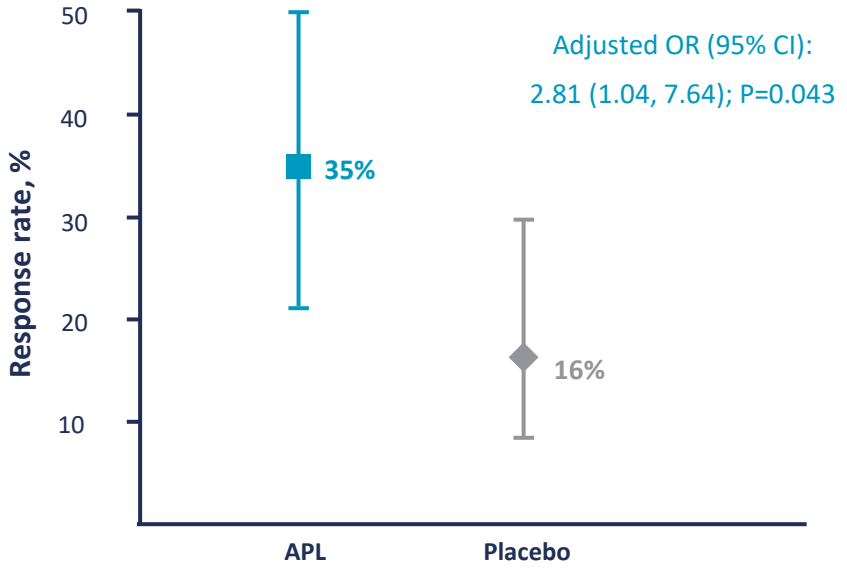
Key secondary endpoint: percentage of patients with a self-rated FULL ON response within 30 minutes at Week 12

The study met its key secondary endpoint:

percentage of patients with a self-rated FULL ON response within 30 min at Week 12



CI, confidence interval; OR, odds ratio.
Olanow CW, et al. Lancet Neurol. 2020; 19: 135–144.

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What were the results of the open-label, dose-titration phase of the pivotal study (CTH-300) of APL for the treatment of OFF episodes in Parkinson's disease?

CTH-300 study design*[1,2]

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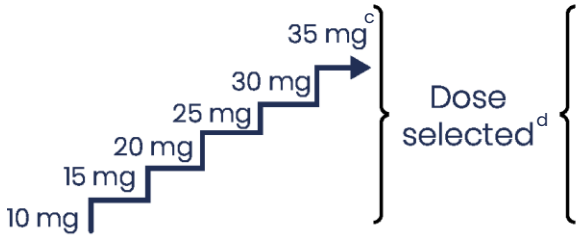
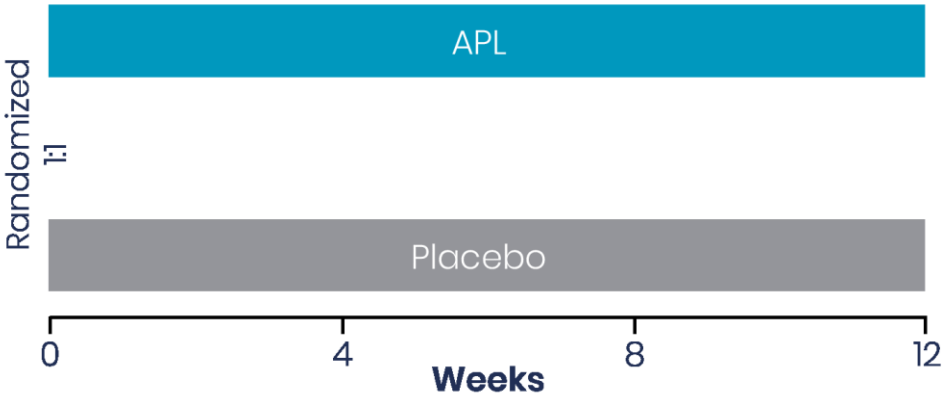


Double-blind maintenance phase



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1. Olanow CW et al. Lancet Neurol. 2020;19:135–144; 2. Hui JS, et al. Parkinsonism Relat Disord 2020;79:110–116.

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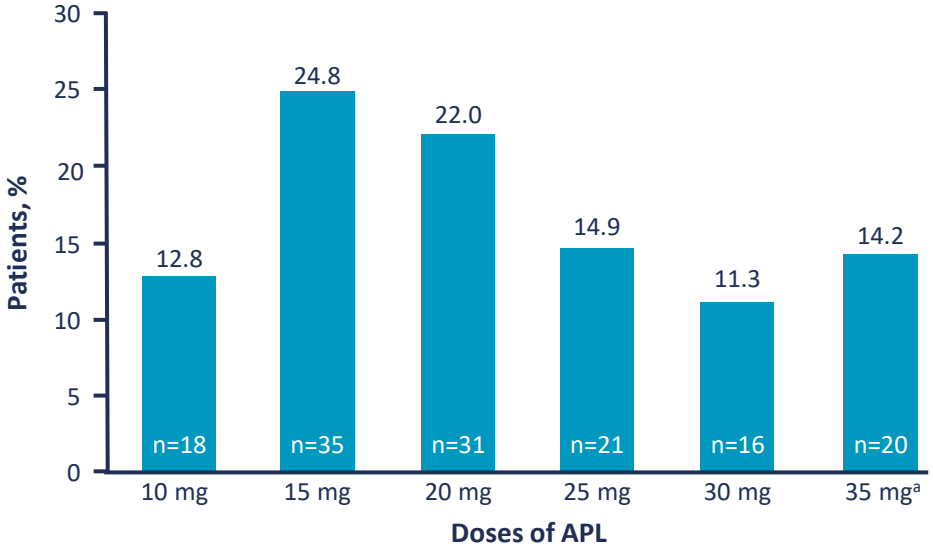
Dose distribution

- 66.1% of randomized patients (n = 109) had their dose successfully titrated within the first 3 APL doses during the dose titration phase
- 32 patients discontinued treatment during titration

Dose distribution of the highest dose of APL received during the open-label titration phase (N=141)



[a]The 35-mg dose (the highest dose studied) was given as 2 sublingual films consisting of 20 mg followed by 15 mg.

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

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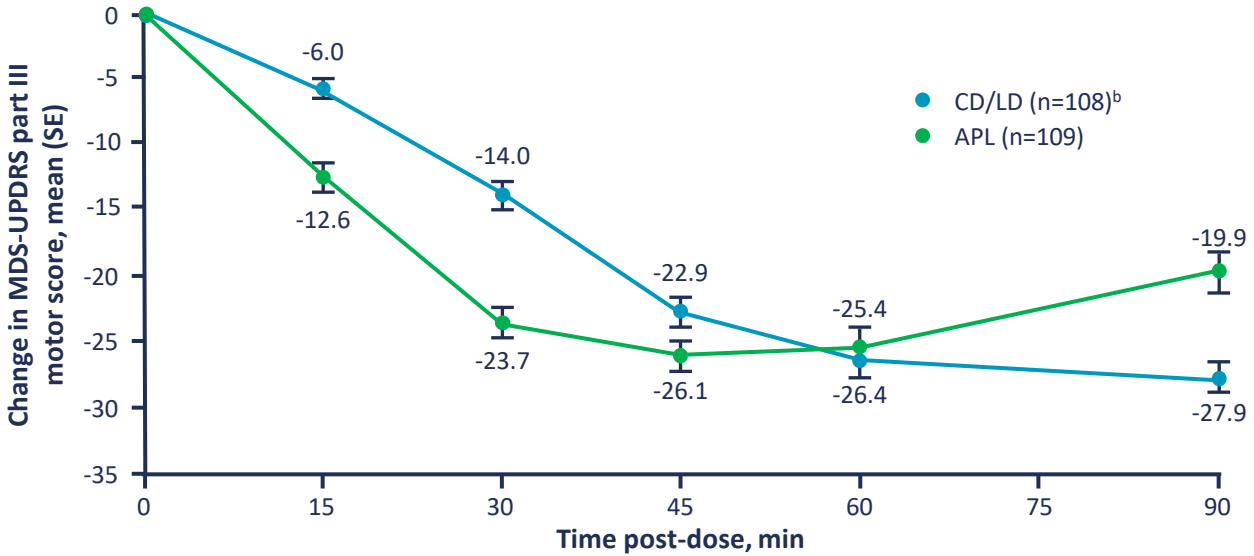
Change from pre-dose in MDS-UPDRS part III score for APL and carbidopa/levodopa (CTH-300 post hoc analysis)[a]



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 CD/LD and the dose of CD/LD administered at screening was the first dose of patients' normal daily maintenance therapy; the dose of CD/LD was not titrated during screening.

[b]CD/LD data were missing for 1 patient.

CD/LD, carbidopa/levodopa.

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

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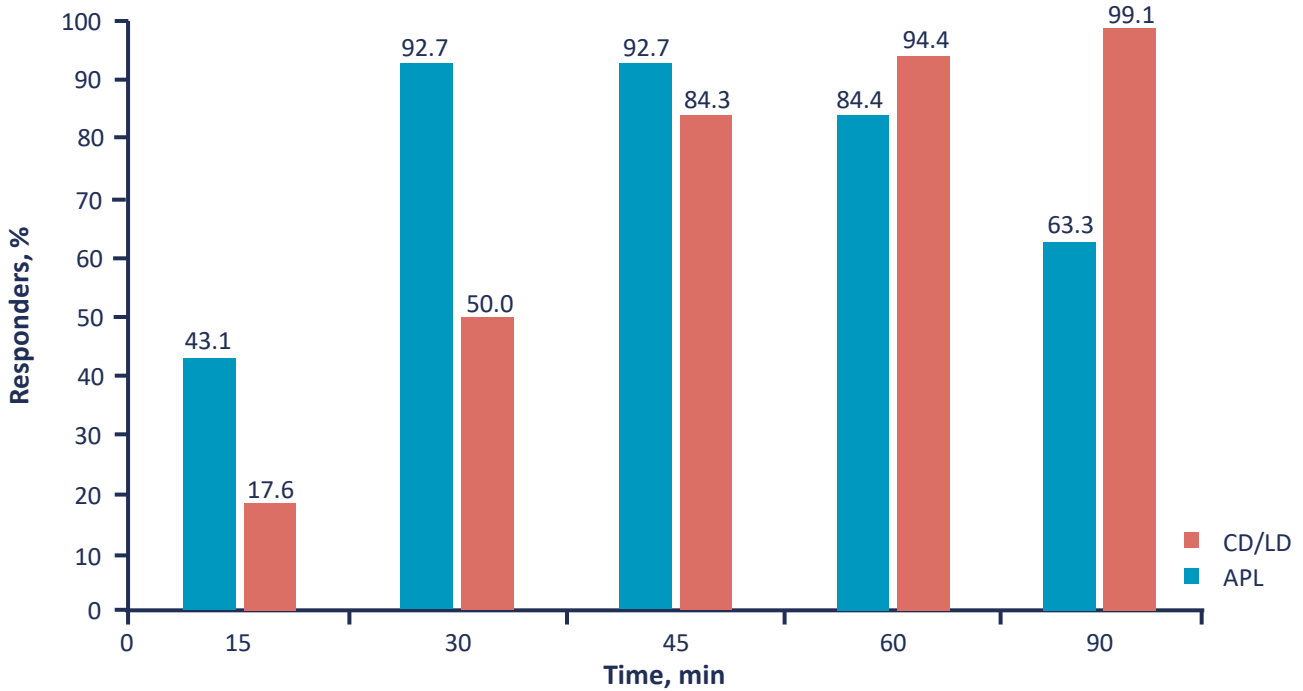
Responder analysis[a]



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[a]Responders were defined as patients with a ≥30% decrease in Movement Disorder Society Unified Parkinson's Disease Rating Scale Part III score from pre-dose to 15, 30, 45, 60, and 90 minutes postdose. During the screening phase levodopa challenge, patients received their usual morning dose of CD/LD following confirmation of an OFF episode (n=108; 1 patient had missing CD/LD data). During the open-label titration phase, patients were titrated to the dose of apomorphine sublingual film (10–35 mg) that provided a FULL ON (n=109).

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

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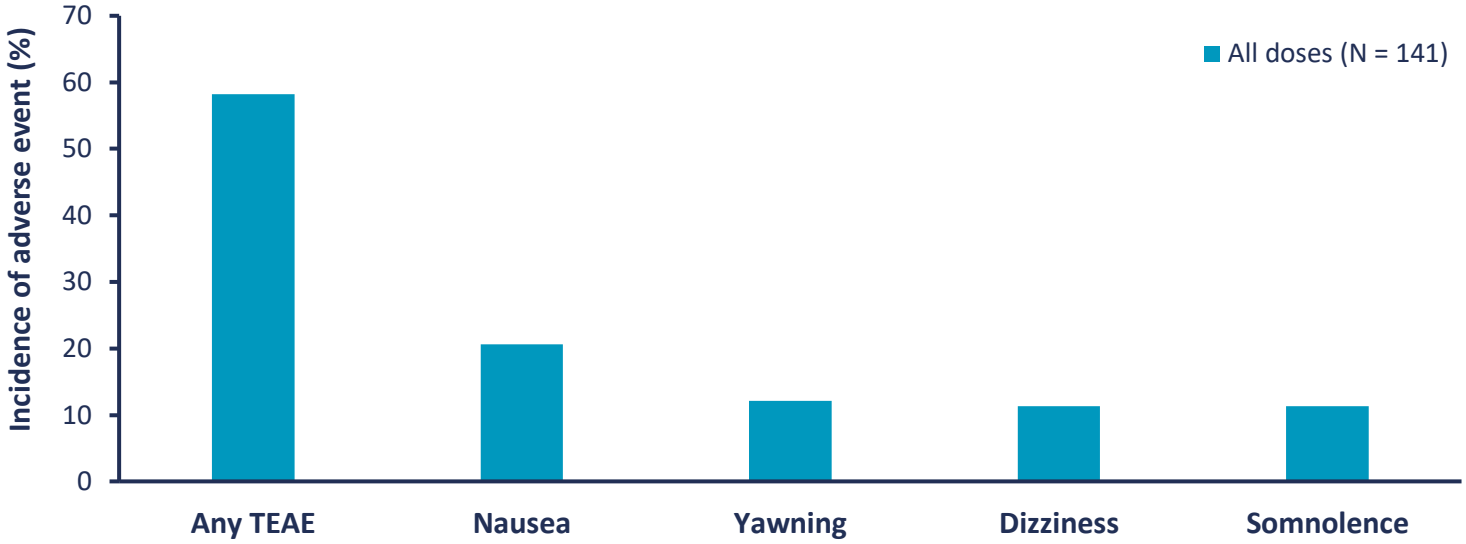
Treatment emergent adverse events (≥10%) during the open-label titration phase



TEAE, treatment-emergent adverse event.
Hui JS, et al. Parkinsonism Relat Disord 2020;79:110–116.

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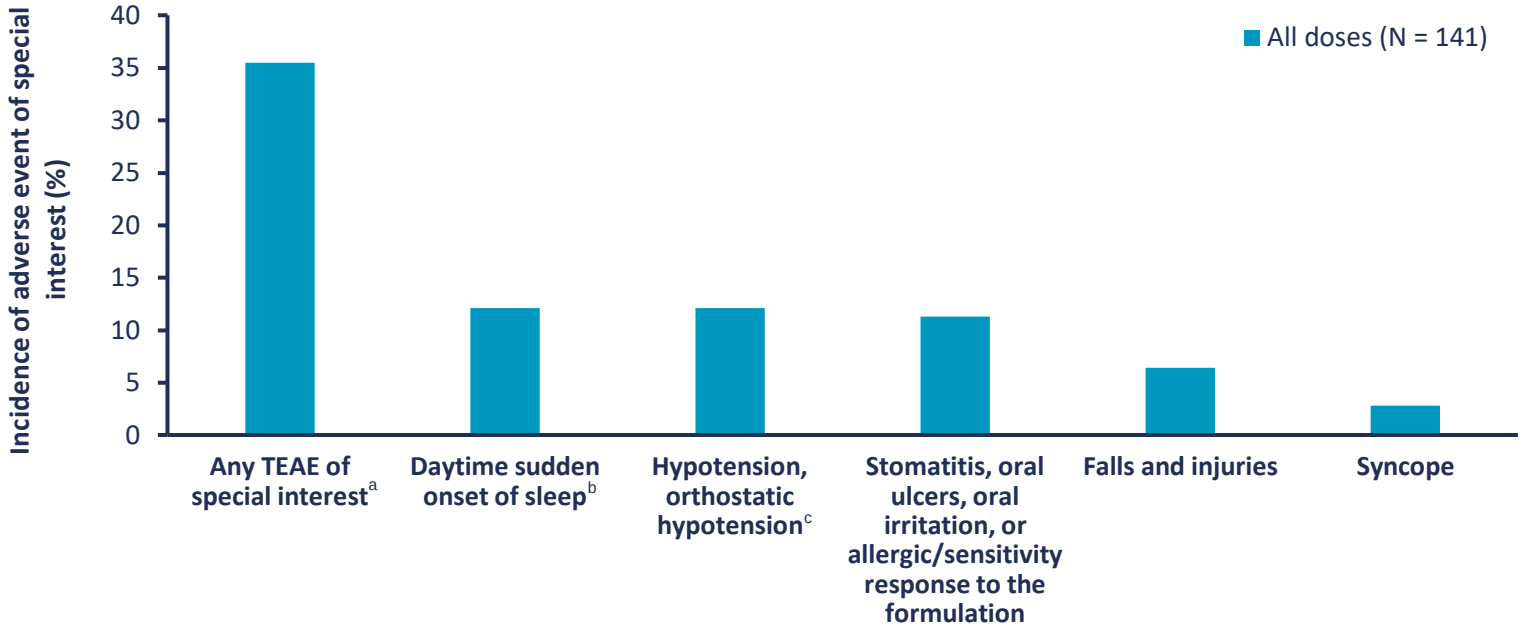
Adverse events of special interest during the open-label titration phase (≥2%)



[a]Patients may have reported more than 1 TEAE; [b]Somnolence was reported in all patients except in 1 patient who reported insomnia at 35 mg; [c]Orthostatic hypotension was reported in one patient each at 10 mg and 15 mg.
Hui JS, et al. Parkinsonism Relat Disord 2020;79:110–116, Supplemental Material, pg 7.

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How will the results of the pivotal study of APL (CTH-300) change the way you treat OFF episodes in patients with Parkinson's disease?

Approved on-demand therapies for OFF episodes in Parkinson's disease

Drug Name	Delivery Route	Indication
Apomorphine hydrochloride injection; SC-APO **APOKYN®[1]** **MOVAPO®, MOVAPO® PFS[2]** **APO-GO® PEN[3]** **APOMINE®, APOMINE® PFS[4]**	Subcutaneous injection	The acute, intermittent treatment of hypomobility, OFF episodes (end-of-dose wearing OFF and unpredictable ON/OFF episodes) associated with advanced PD
Levodopa inhalation powder; CVT-301 **INBRIJA™ [5,6]**	Oral inhalation	The intermittent treatment of OFF episodes in patients with PD treated with carbidopa/levodopa
Apomorphine sublingual film; APL-130277; APL **KYNMOBI™ [7]**	Sublingual film	The acute, intermittent treatment of OFF episodes in patients with PD

SC-APO, subcutaneous apomorphine.

1. APOKYN® (apomorphine hydrochloride injection) [Prescribing information]. Louisville, KY, USA: US WorldMeds, LLC; 2020. 2. MOVAPO® and MOVAPO® PFS (apomorphine hydrochloride hemihydrate) [Consumer Medicine Information]. Dandenong, Australia: STADA Pharmaceuticals Australia Pty Ltd; 2019. 3. APO-go® PEN [Summary of Product Characteristics]. Berkshire, UK: Britannia Pharmaceuticals Ltd; 2020. 4. APOMINE® and APOMINE® PFS (apomorphine hydrochloride) [Consumer Medicine Information]. Melbourne, Australia: Hospira Australia Pty Ltd; 2015. 5. INBRIJA® (levodopa inhalation powder) [Prescribing information]. Ardsley, NY, USA: Acorda Therapeutics, Inc; 2019. 6. INBRIJA® (levodopa inhalation powder) [Summary of Product Characteristics]. Dublin, Ireland: Acorda Therapeutics Ireland Limited; 2019. 7. KYNMOBI™ (apomorphine hydrochloride) sublingual film [Prescribing information]. Marlborough, MA, USA: Sunovion Pharmaceuticals Inc; 2020.

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