Supplementary Material

Dose Optimization of Apomorphine Sublingual Film for OFF Episodes in Parkinson's Disease: Is the Prophylactic Use of an Antiemetic Necessary?

Supplementary Table 1
Key eligibility criteria

Patient Population	Key Inclusion Criteria	Key Exclusion Criteria

New patients[a]	• Idiopathic PD by UK Brain Bank criteria
	• Stage 1–3 by modified Hoehn and Yahr scale when ON
	• MMSE score >25
	• Clinically meaningful response to CD/LD with well-defined early morning OFF episodes, as determined by the investigator
	  ○ Receiving stable doses of CD/LD and adjunctive PD medications for ≥4 weeks (MAO-B inhibitors must be stable for ≥8 weeks) before first screening visit
	• ≥1 OFF episode per day with total daily OFF time of ≥2 h
		• Atypical or secondary parkinsonism
		• Major psychiatric disorder
		• Mouth cankers/sores within 30 days of the first screening visit
		• Previous treatment with:
		  ○ Deep brain stimulation
		  ○ Intraduodenal levodopa
		  ○ Continuous SC-APO infusion
		  ○ SC-APO within 7 days of the first screening visit
		• Currently taking:
		  ○ 5-HT_3 antagonists
		  ○ Dopamine antagonists (excluding quetiapine or clozapine)
		  ○ Dopamine-depleting agents

Rollover patients[b]	• Completed a prior SL-APO study and would benefit from continued treatment[c] • No major changes in concomitant PD medications from prior study	• Mouth cankers/sores within 14 days of completing a previous SL-APO study • Patients were excluded from the original CTH-201 (NCT03187301) study if they experienced nausea associated with the use of dopamine agonists that required treatment with an antiemetic

[a]New patients had no prior exposure to SL-APO; [b]Rollover patients had completed a prior SL-APO study (NCT03187301, NCT03292016, NCT02469090, or NCT03391882); [c]Based on investigator opinion. 5-HT_3, 5-hydroxytryptamine type 3; CD/LD, carbidopa/levodopa; MAO-B, monoamine oxidase-B; MMSE, Mini-Mental State Examination; PD, Parkinson's disease; SC-APO, subcutaneous apomorphine; SL-APO, apomorphine sublingual film.

Supplementary Table 2

Antiemetic use during dose optimization and concomitant PD medications at baseline[a]

Characteristic	Overall (N=449)	US (*n*=391)	Outside US (*n*=58)
Antiemetic use, *n* (%)[b]	253 (56.3)	210 (53.7)	43 (74.1)
Domperidone	43 (17.0)	0	43 (100)
Trimethobenzamide	207 (81.8)	207 (98.6)	0
Domperidone/trimethobenzamide[c]	3 (1.2)	3 (1.4)	0
Concomitant PD medications, *n* (%)[d]			
Dopamine agonists	271 (60.4)	221 (56.5)	50 (86.2)
MAO-B inhibitors	202 (45.0)	169 (43.2)	33 (56.9)
Amantadine	100 (22.3)	87 (22.3)	13 (22.4)

[a]Titration population (all patients who enrolled in the study and received ≥1 dose of study medication during the titration phase); [b]Patients used an antiemetic during dose optimization; [c]Patients used domperidone and trimethobenzamide during dose optimization but details regarding timing of use for each agent is unknown; [d]Defined as medication use overlapping with the first dose of SL-APO during dose optimization. MAO-B, monoamine oxidase-B; PD, Parkinson's disease; SL-APO, apomorphine sublingual film.

Supplementary Table 3

Demographics and baseline disease characteristics of new patients enrolled after prophylactic antiemetic use was made optional and who did and did not use an antiemetic[a]

Characteristic	Used an Antiemetic[b] (*n*=34)	Did Not Use an Antiemetic[b] (*n*=154)	Overall (*n*=188)
Age, y, mean (SD)	63.0 (10.8)	64.5 (8.3)	64.3 (8.8)
Male, *n* (%)	18 (52.9)	103 (66.9)	121 (64.4)
Race, *n* (%)			
White	34 (100)	147 (95.5)	181 (96.3)
Black or African American	0	5 (3.2)	5 (2.7)
Other	0	2 (1.3)	2 (1.1)
Weight, kg, mean (SD)	81.8 (19.7)	81.4 (16.4)	81.5 (17.0)
Time since PD diagnosis, y, mean (SD)	8.2 (5.3)	8.3 (4.8)	8.3 (4.9)
Time since motor fluctuations, y, mean (SD)	4.6 (3.6)	4.5 (4.0)	4.5 (3.9)
Modified Hoehn and Yahr stage when ON, *n* (%)			
0	0	1 (0.6)	1 (0.5)
1 or 1.5	2 (5.9)	7 (4.5)	9 (4.8)
2 or 2.5	26 (76.5)	131 (85.1)	157 (83.5)
3	4 (11.8)	12 (7.8)	16 (8.5)
4	0	1 (0.6)	1 (0.5)
Missing	2 (5.9)	2 (1.3)	4 (2.1)
Number of OFF episodes per day, mean (SD)	4.3 (1.9)	4.1 (1.4)	4.1 (1.5)
Total daily levodopa dose, mg, median	800.0	837.5	800.0
Concomitant PD medications, *n* (%)[c]			
Dopamine agonists	12 (35.3)	91 (59.1)	103 (54.8)
MAO-B inhibitors	16 (47.1)	70 (45.5)	86 (45.7)
Amantadine	4 (11.8)	36 (23.4)	40 (21.3)

[a]Safety population (all patients who enrolled in the study and received ≥1 dose of study medication; [b]Population was comprised entirely of US patients and therefore trimethobenzamide was the only antiemetic available for use; [c]Defined as medication use overlapping with first dose of SL-APO during dose optimization. MAO-B, monoamine oxidase-B; PD, Parkinson's disease; SL-APO, apomorphine sublingual film.

Supplementary Table 4

TEAEs occurring in ≥2% of patients overall in the dose-optimization phase[a]

Parameter, *n* (%)	Used an Antiemetic (*n*=253)	Did Not Use an Antiemetic (*n*=196)	Overall (N=449)
Overall	143 (56.5)	89 (45.4)	232 (51.7)
Yawning	26 (10.3)	17 (8.7)	43 (9.6)
Somnolence	16 (6.3)	14 (7.1)	30 (6.7)
Dizziness	16 (6.3)	11 (5.6)	27 (6.0)
Headache	19 (7.5)	4 (2.0)	23 (5.1)
Fatigue	14 (5.5)	4 (2.0)	18 (4.0)
Oral mucosal erythema	12 (4.7)	5 (2.6)	17 (3.8)
Orthostatic hypertension	7 (2.8)	6 (3.1)	13 (2.9)
Dyskinesia	5 (2.0)	7 (3.6)	12 (2.7)
Hypertension	8 (3.2)	3 (1.5)	11 (2.4)

[a]Dose-optimization population (all patients who enrolled in the study and received ≥1 dose of study medication during the dose-optimization phase). TEAE, treatment-emergent adverse event.

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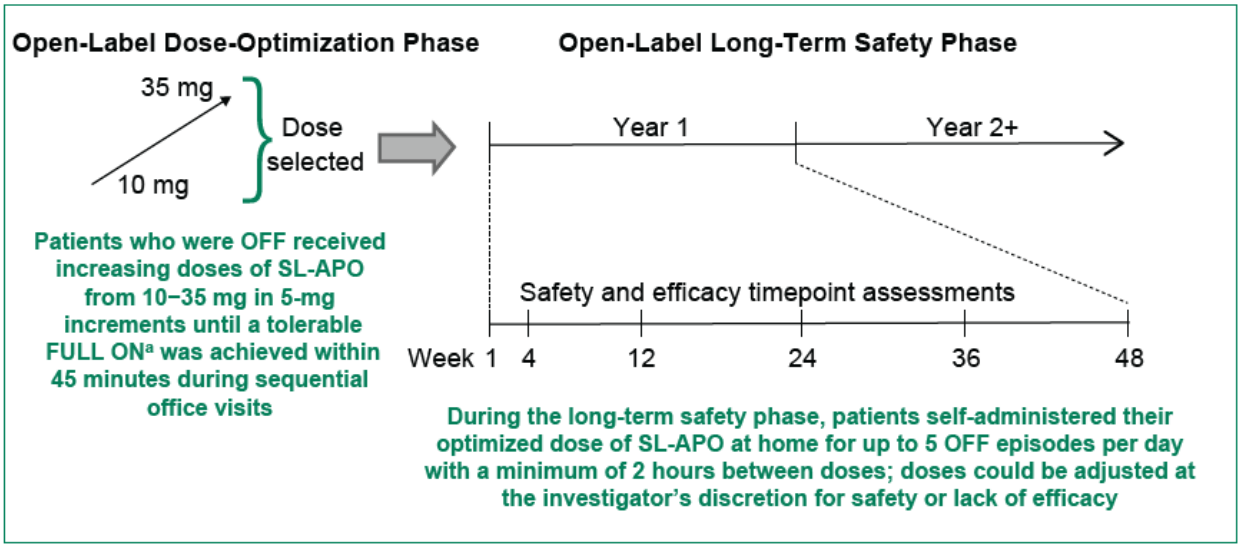
Supplementary Figure 1. Study design



[a]FULL ON was patient- and investigator-assessed and defined as response that provided the patient with benefit related to mobility, stiffness, and slowness; adequate motor function to perform normal daily activities; and a response that was comparable to or better than the normal response to their Parkinson's disease medications before enrolling in the study.
SL-APO, apomorphine sublingual film.