Oropharyngeal adverse events in people with Parkinson's disease and motor fluctuations treated with apomorphine sublingual film

Elisa Andrenelli[1], Lars Wojtecki[2,3], Fradique Moreira[4], Esther Cubo[5], Miguel M. Fonseca[6], Glynn Harrison-Jones[6], Carmen Denecke Muhr[6]

[1]Dept. of Experimental and Clinical Medicine, Politecnica delle Marche Univ., Ancona, Italy; [2]Dept. of Neurology & Inst. of Clinical Neuroscience, Univ. Clinic Duesseldorf, Germany; [3]Dept. of Neurology & Neurorehabilitation, Hospital Zum Heiligen Geist, Teaching Hosp. of Heinrich-Heine-Univ., Kempen, Germany; [4]Centro Hospitalar Univ. Coimbra, Coimbra, Portugal; [5]Dept. of Geriatrics, Hospital Univ. Burgos, Spain; [6]Bial – Portela & Ca, S.A., Coronado, Portugal

BACKGROUND

Sublingual apomorphine film (SL-APO) is an on-demand treatment for OFF episodes in Parkinson's disease (PD) with proven efficacy and tolerability (CTH-300 trial).

Objective

To describe oropharyngeal (OP) treatment-emergent adverse events (TEAEs) with SL-APO and identify risk factors for discontinuation.

METHODS

This post hoc analysis used data from CTH-301, an open-label, multicenter, non-randomized Phase 3 trial with a dose-optimization period followed by a long-term safety (LTS) phase. The objectives were to evaluate:

- The incidence, severity, and time to onset of oropharyngeal (OP) treatment-emergent adverse events (TEAEs) and related discontinuations;
- Changes in TEAE severity during the LTS phase;
- The relationship between daily SL-APO dose and OP TEAEs;
- Baseline differences between patients with and without OP TEAEs and between those who discontinued treatment due to OP TEAEs and those who continued.

RESULTS

Population:

496 patients enrolled (127 rollover)

Oropharyngeal TEAEs: incidence, severity and onset

- During the dose-optimization and long-term safety (LTS) phases, 41.5% of patients in the safety population experienced oropharyngeal (OP) TEAEs, and 16.3% discontinued treatment because of them (Table 1)
- Most OP TEAEs, including those causing discontinuation, were mild or moderate; severe events were rare but linked to higher discontinuation rates. No OP TEAE–related deaths occurred. The most frequent causes of discontinuation (>2%) were lip swelling, mouth ulceration, and stomatitis. Median time to first OP TEAE was 89.5 days. (Figure 1)

Changes in TEAE severity during the LTS phase

- Most OP TEAEs during the LTS phase resolved (92.1%), with a median spontaneous resolution time of 12 days. Most events were mild (63.8%) or moderate (34.4%) and did not worsen (≈67%). Severe events were uncommon and often improved to milder severity. (Table 2)

Correlation between daily SL-APO dose and OP TEAEs

- Higher SL-APO dose associated with increased OP TEAEs incidence (38.3 vs 32.1 mg/day; p=0.024).

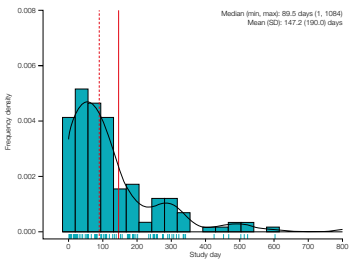
Risk factors:

- OP TEAEs were associated with concomitant dopamine agonist use (p<0.001), older age (p<0.01), and other dopaminergic medications (p<0.01). Discontinuations due to OP TEAEs were linked to older age (p<0.01) and dopamine agonist use (p=0.042). (Figure 2)

DISCUSSION AND CONCLUSION:

- OP TEAEs were mostly mild or moderate, occurred early, and were reversible.
- Severe events were rare and transient.
- Discontinuations were mainly due to lip swelling, ulceration, and stomatitis.
- Risk factors: higher daily dose, older age, dopamine agonist use.
- Early monitoring and proactive management may limit discontinuations.

Figure 1. Distribution of days to onset of the first oropharyngeal TEAEs during the dose-optimisation phase and the LTS phase of Study CTH-301



Black lines indicate smoothed density estimate of the histograms; turquoise vertical lines on x-axes indicate days to onset of oropharyngeal TEAEs or discontinuation due to oropharyngeal TEAEs for each individual patient; dashed red lines indicate the mean.

LTS, long-term safety; SD, standard deviation; TEAEs, treatment-emergent adverse events

Table 2. Number of patients transitioning from milder to more advanced oropharyngeal TEAE severity

Initial severity	Subsequent states of severity		
	Mild n (%)	Moderate n (%)	Severe n (%)
No TEAE	104 (63.8)	56 (34.4)	3 (1.8)
Mild	56 (66.7)	27 (32.1)	1 (1.2)
Moderate	18 (30.0)	40 (66.7)	2 (3.3)
Severe	1 (25.0)	3 (75.0)	0 (0.0)

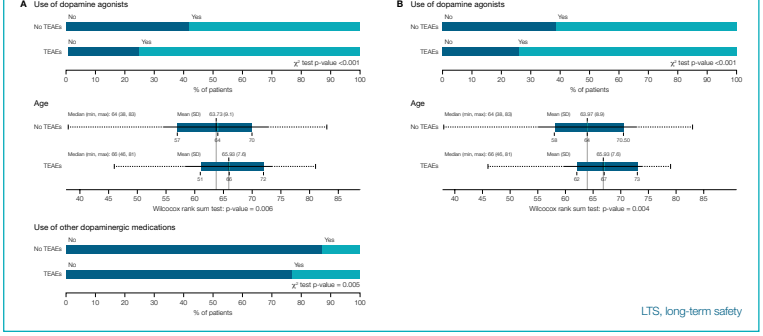
The states refer to the overall oropharyngeal TEAE profile of a patient. The severity of the state is determined by the most severe status observed during the study period. TEAE, treatment-related adverse event

Table 1. Summary of oropharyngeal TEAEs during the dose-optimisation phase and the LTS phase of Study CTH-301

	Dose-optimisation phase n=449	LTS phase n=426	Dose-optimisation and LTS phase (safety population) N=496
All TEAEs			
Any TEAEs, n (%); number of events	232 (51.7); 657	365 (85.7); 1966	446 (89.9); 2623
Oropharyngeal TEAEs			
Any oropharyngeal TEAEs n (%); number of events	53 (11.8); 78	178 (41.8); 475	206 (41.5); 553
Drug-related TEAEs, n (%); number of events	25 (5.6); 36	145 (34.0); 394	160 (32.3); 430
Mild*	20 (4.5); 30	67 (15.7); 141	79 (15.9); 168
Moderate*	5 (1.1); 5	72 (16.9); 148	75 (15.1); 152
Severe*	0	6 (1.4); 8	6 (1.2); 8
TEAEs leading to drug reduction, n (%); number of events	1 (0.2); 1	7 (1.6); 13	8 (1.6); 14
TEAEs leading to drug interruption, n (%); number of events	0	45 (10.6); 72	45 (9.1); 72
TEAEs leading to drug discontinuation, n (%); number of events	1 (0.2); 1	80 (18.8); 137	81 (16.3); 138
Mild*	1 (0.2); 1	24 (5.6); 31	25 (5.0); 32
Moderate*	0	52 (12.2); 81	52 (10.5); 81
Severe*	0	4 (0.9); 5	4 (0.8); 5
Most common (≥2%) TEAEs leading to drug discontinuation, n (%); number of events			
Lip swelling		19 (4.5); 19	
Mouth ulceration		11 (2.6); 13	
Stomatitis	–	10 (2.3); 10	–
TEAEs leading to death, n (%); number of events	0	0	0

*Based on the highest severity level for each patient; LTS, long-term safety; TEAE, treatment-emergent adverse event

Figure 2. Baseline variables associated with the occurrence of oropharyngeal TEAEs (A) and oropharyngeal TEAEs leading to discontinuation (B) in the dose-optimisation phase and the LTS phase of Study CTH-301



LTS, long-term safety

REFERENCES

1. Titova N, Chaudhuri KR. Parkinsonism Relat Disord. 2016;33(Suppl1):S56-S60;
2. Olanow CW, et al. Lancet Neurol. 2020;19(2):135–144;
3. Kassubek J, et al. J Neurol. 2024;271(6):35.

This study was supported by Bial.