Baseline Variables Associated with Apomorphine Sublingual Film Retention

Laura Vacca[1], Jan Kassubek[2,3], Johannes Schwarz[4], Lydia López Manzanares[5], Miguel M. Fonseca[6], Carmen Denecke Muhr[6]

[1]Clinical Trial Centre - IRCCS San Raffaele – Rome ; [2]Department of Neurology, University Hospital Ulm, Ulm, Germany; [3]German Centre for Neurodegenerative Diseases, Ulm, Germany; [4]Department of Geriatrics, Kreisklinik Ebersberg, Ebersberg, Germany; [5]La Princesa University Hospital, Madrid, Spain; [6]Bial – R&D Investments, S.A., Coronado, Portugal

Introduction

- Patients with Parkinson's disease (PD) often develop fluctuations characterised by alternating ON and OFF episodes,[1–3] with OFF episodes manifesting as both motor and non-motor symptoms and affecting the quality of life of patients[2,3]
- Subcutaneous apomorphine (APO, a dopamine agonist) is an efficacious rescue therapy for the treatment of individual OFF episodes, but the need for injection is a barrier to its wider use among patients with PD and motor fluctuations[2–4]
- To overcome the limitations associated with injection, a sublingual formulation (SL-APO) has been developed
- SL-APO has been shown to be generally well tolerated and efficacious as an on-demand treatment for OFF episodes in PD patients in a 12-week, double-blind, placebo-controlled Phase 3 trial[2]
- Study CTH-301 demonstrated the efficacy and safety of SL-APO for the treatment of OFF episodes in patients with PD over the long term[3]
- The aim of this *post-hoc* analysis of Study CTH-301 was to identify baseline variables that differ between patients who completed the study and those who discontinued due to either lack of efficacy or adverse events (AEs), therefore influencing retention

Methods

Study design and patient population

- Study CTH-301 was a Phase 3, multicentre, non-randomised, open-label study that assessed the safety, tolerability and efficacy of SL-APO when used as an on-demand treatment for OFF episodes over the long term (>2 years)
  - It consisted of a 3-week open-label dose-optimisation phase and an open-label long-term safety phase
  - Both treatment naïve patients defined as '*de novo* patients' and 'rollover patients' who had completed a previous SL-APO study (CTH-201, CTH-203, CTH-300, or CTH-302) were included
  - All patients received SL-APO over the dose range 10–35 mg, with dose optimisation based on efficacy, safety and tolerability
- Patients with a clinical diagnosis of idiopathic PD, a clinically meaningful response to levodopa, stage 1–3 on the modified Hoehn and Yahr scale in ON state, at least one OFF episode per day, and a total daily OFF time of ≥2 hours treated with stable doses of levodopa/carbidopa and adjunctive PD medications were included[3]

Study assessments

- The primary endpoint of Study CTH-301 was the safety and tolerability of SL-APO during the long-term safety phase, assessed by evaluating AEs
- In this *post-hoc* analysis, data from Study CTH-301 were used to build a model to identify baseline variables that best predict who would complete the study (completers) and those who would discontinue during the dose-optimisation or long-term safety phase (non-completers) due to either lack of efficacy or AEs

Statistical model

- Variable ranking: normalised baseline variables, along with three random ones as reference for noise, were selected based on their correlation (Chi-square) with the discrete target (completers vs non-completers due to lack of efficacy or AEs)
- Feature selection process: baseline variables with rankings higher than the first random one were selected for the final model
- Method for final model: a logistic regression classification algorithm with LASSO (L1) regularisation cost strength of 1 and balanced class distribution (weight classes inversely proportional to their frequencies) was used to identify the baseline variables that best predict who would complete the study. The selected variables were compared between completers and non-completers due to lack of efficacy or AEs respectively.

Results

Study population

- Overall, 496 patients entered the dose-optimisation phase (**Table 1**)[3]
  - The mean age of the overall population was 64.4 years, the mean time since PD diagnosis was 8.7 years, and the mean time since the onset of motor fluctuations was 4.5 years. The most common types of OFF episodes were wearing-off (96.8%), delayed ON (69.2%) and morning akinesia (64.9%). The mean number of OFF episodes per day at baseline was 3.9 with a mean duration of 75.3 min
  - Demographic and baseline disease characteristics were generally comparable between the *de novo* (n=369) and rollover (n=127) subgroups
- In total, 120 patients completed the study, 26 discontinued due to lack of efficacy, 167 due to AEs, and 183 due to other reasons
  - Patients who entered the long-term safety phase remained on their optimised SL-APO dose for a median of 169.0 days (25th, 75th percentile: 82.0, 437.8) (**Figure 1**)

Baseline variables associated with discontinuation due to lack of efficacy

- A total of four baseline variables that best predict who would complete the study were selected: total daily dose of levodopa, morning akinesia, prior exposure to SL-APO and number of daily levodopa intakes
- All four variables were significantly different between completers and non-completers due to lack of efficacy (**Figure 2**). Compared with non-completers due to a lack of efficacy, completers reported:
  - A lower total daily dose of levodopa (p<0.001)
  - A higher rate of morning akinesia (p=0.036)
  - A lower rate of *de novo* enrolment (p=0.048)
  - A lower number of daily levodopa intakes (p=0.027)

Baseline variables associated with discontinuation due to AEs

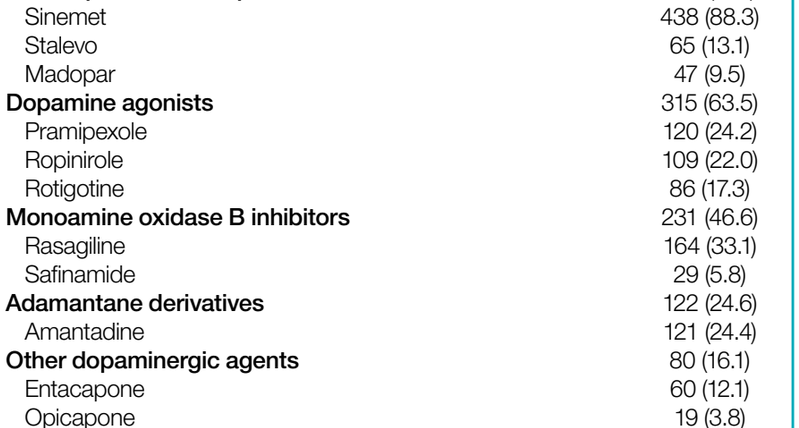
- A total of three baseline variables that best predict who would complete the study were selected: concomitant dopamine agonist use, prior exposure to SL-APO and age
- Of these variables, two differed significantly between completers and non-completers due to AEs (**Figure 3**). Compared with non-completers due to AEs, completers had a higher rate of concomitant dopamine agonists use (p<0.001) and a lower incidence of *de novo* enrolment (p=0.019) (**Figure 3**)
- Completers were on average younger than non-completers, but the difference was not significant (p=0.05) (**Figure 3**)

Table 1. Patient demographic and baseline characteristics, and use of concomitant PD medications used as variables to feed the model

	Total population N=496
Age, years	
Mean (SD)	64.4 (8.7)
Median (min, max)	65.0 (38, 83)
Sex, n (%)	
Male	333 (67.1)
Female	163 (32.9)
Race, n (%)	
White	478 (96.4)
Black or African American	10 (2.0)
Asian	4 (0.8)
American Indian or Alaska Native	1 (0.2)
Native Hawaiian or Other Pacific	1 (0.2)
Other	2 (0.4)
Time since PD diagnosis, years	
Mean (SD)	8.7 (4.5)
Median (min, max)	8.0 (0.5, 27.0)
Time since motor fluctuations started, mean (SD) years	4.5 (3.7)[a]
Type of OFF episodes experienced, n (%)	
Wearing-off	480 (96.8)
Delayed ON	343 (69.2)
Morning akinesia	322 (64.9)
Dose failure	218 (44.0)
Sudden OFF	212 (42.7)
Number of OFF episodes typically experienced/day, mean (SD)	3.9 (1.3)[a]
Typical duration of OFF episodes, mean (SD) minutes	75.3 (53.8)
Modified Hoehn and Yahr score (ON state), n (%)	
0-1.5	23 (4.6)
2-2.5	296 (59.7)
≥3	43 (8.7)
Missing	134 (27.0)
MDS-UPDRS Part III score in OFF state prior to levodopa administration at screening	
n	367
Mean (SD)	42.0 (14.6)
Median (min, max)	42.0 (11, 87)
Total daily levodopa dose, mg	1097.7 (802.2)[b]
Use of ≥1 concomitant PD medication,[c] n (%)	496 (100)
Most commonly used[d] concomitant PD medications,[c] n (%)	
Levodopa and levodopa derivatives	496 (100)
Sinemet	438 (88.3)
Stalevo	65 (13.1)
Madopar	47 (9.5)
Dopamine agonists	315 (63.5)
Pramipexole	120 (24.2)
Ropinirole	109 (22.0)
Rotigotine	86 (17.3)
Monoamine oxidase B inhibitors	231 (46.6)
Rasagiline	164 (33.1)
Safinamide	29 (5.8)
Adamantane derivatives	122 (24.6)
Amantadine	121 (24.4)
Other dopaminergic agents	80 (16.1)
Entacapone	60 (12.1)
Opicapone	19 (3.8)
Enrolment group, n (%)	496 (100)
De novo	369 (74.4)
Rollover	127 (25.6)
Total number of daily levodopa intakes, median (min, max)	5 (3, 18)

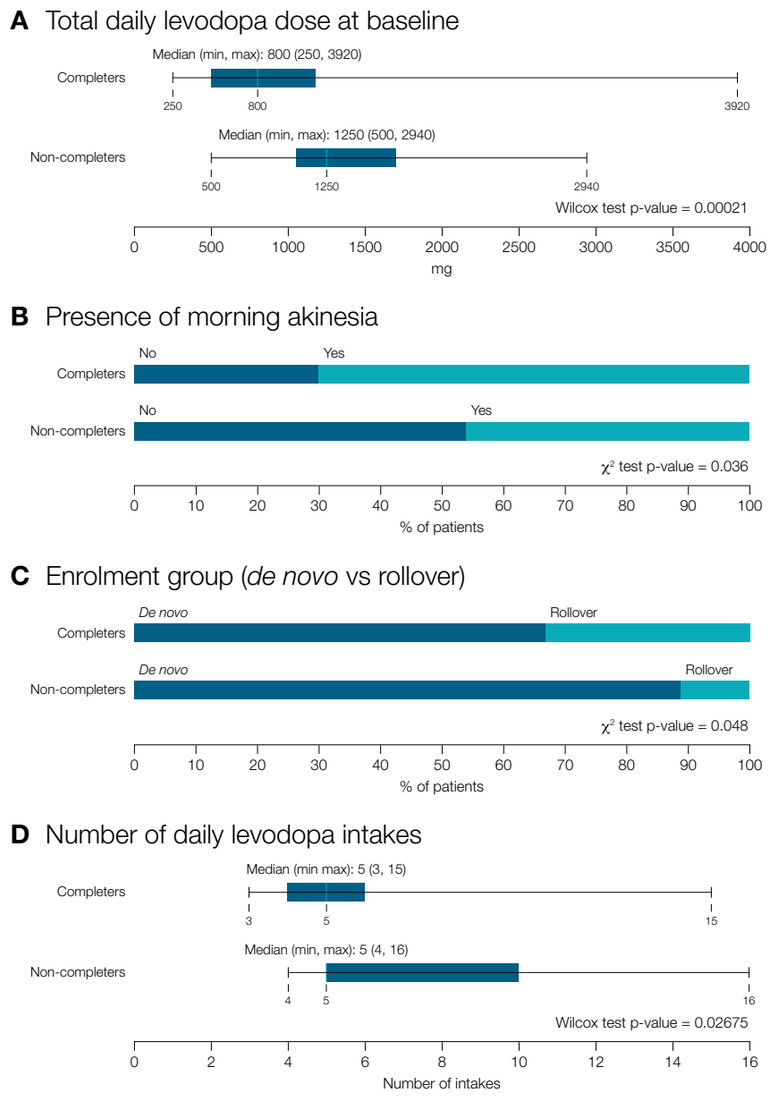
Note: N=496 for total population unless otherwise stated.
[a]N=494; [b]N=481; [c]Concomitant PD medications were those with a start or stop date on or after the first date of study drug dosing; [d]≥10% of *de novo* or rollover patients. max, maximum; MDS-UPDRS, Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale; min, minimum; PD, Parkinson's disease; SD, standard deviation.

Figure 1. Distribution of days to discontinuations during the long-term safety phase of Study CTH-301



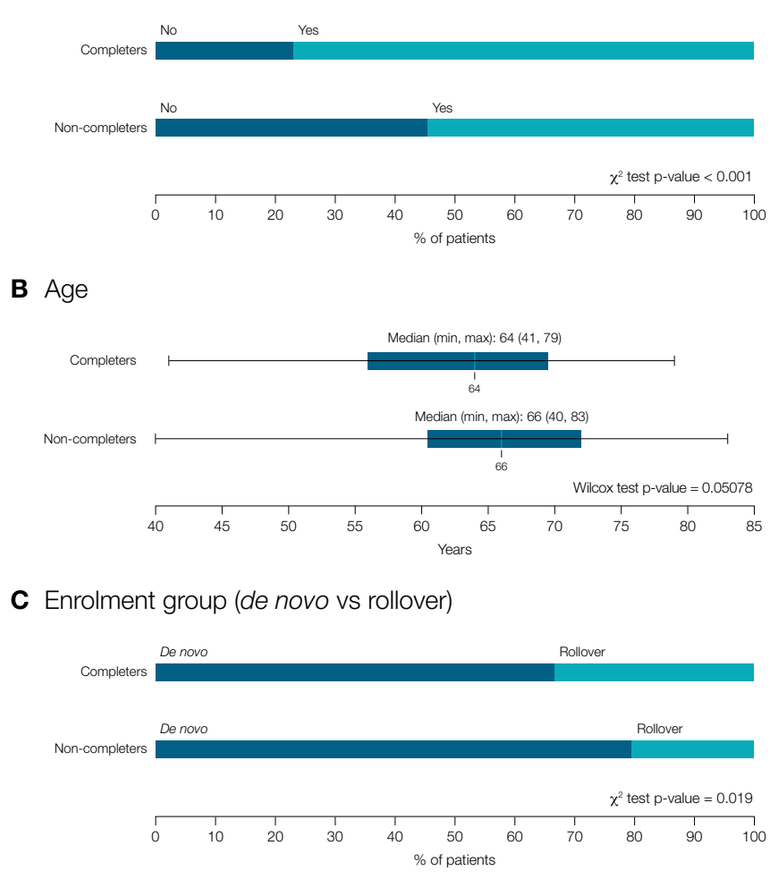
Black lines indicate smoothed density estimate of the histograms; turquoise vertical lines on x-axes indicate discontinuation events for each individual patient; dashed red lines indicate the median; continuous red lines indicate the mean.

Figure 2. Key baseline variables identified for comparison between subgroups of patients who completed the study and those who discontinued due to lack of efficacy: (A) total daily levodopa dose at baseline; (B) presence of morning akinesia; (C) enrolment group (de novo vs rollover*); (D) number of daily levodopa intakes



SD, standard deviation; SL-APO, apomorphine sublingual film

Figure 3. Key baseline variables identified for comparison between subgroups of patients who completed the study and those who discontinued due to adverse events: (A) dopamine agonists use; (B) age; (C) enrolment group (de novo vs rollover*)



SD, standard deviation; SL-APO, apomorphine sublingual film

Conclusion

- **Factors such as the levodopa total daily dose and daily number of intakes, morning akinesia, prior exposure to SL-APO, and the concurrent use of dopamine agonists might influence retention**
- **The findings from this study could assist in identifying patients who are more likely to continue using SL-APO over the long term**

References

1. Ahlskog JE and Muenter MD. *Mov Disord.* 2001;16:448–58; 2. Olanow CW, *et al. Lancet Neurol.* 2019;19:P135–44; 3. Kassubek J, *et al. J Neurol.* 2024 Mar 28. Online ahead of print; 4. Fabbri M, *et al. Neurol Ther.* 2023;12:391–424.

Conflict of Interest

JK has received honoraria or consultation fees from AbbVie, Bial, Biogen, Desitin, Esteve, Licher MT, Medtronic, NeuroDerm, Novartis, STADA, UCB Pharma, and Zambon; in addition, he is Specialty Chief Editor for Frontiers in Neurology (section Applied Neuroimaging) and Associate Editor (Neurology) for Therapeutic Advances in Chronic Disease. JS received honoraria in the past 5 years from UCB, BIAL and AbbVie for presentations and consulting. LLM received honoraria in the past 5 years from Abbott, AbbVie, Bial, Biogen, Esteve, Italfarmaco, Orion, STADA and Zambon. MMF and CDM are employees of Bial. Supported by Bial – Portela & Cª, S.A.