Continuous Subcutaneous Apomorphine Infusion (CSAI) Responder Rates During Titration: Observations from the Open-label Phase 3 InfusON Trial

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Background and Objective

- Apomorphine (like endogenous dopamine), activates both D1-like (D1 and D5) and D2-like (D2, D3, and D4) receptors, which unlike conventional (D2-family predominant) dopamine agonists, is thought to underlie its robust efficacy and lower incidence of adverse effects (such as impulse control disorders).[1]
- Although continuous subcutaneous apomorphine infusion (CSAI) therapy is widely used to treat OFF motor fluctuations in Parkinson disease (PD), it is not yet available in the United States.
- The open-label, phase 3 InfusON trial [NCT02339064] provides US-centric safety and efficacy data to support drug approval.
- Here we evaluate responder rates in the InfusON trial during initial CSAI titration.

Methods

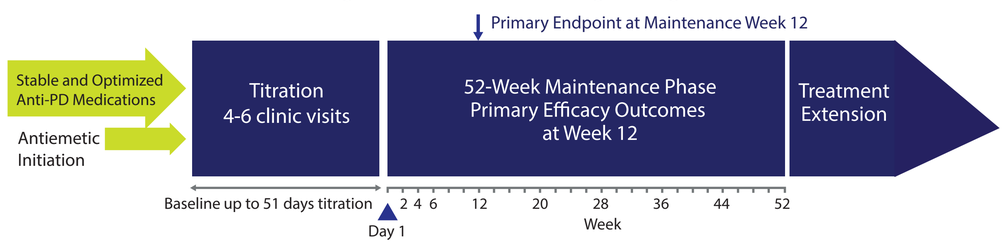
- Outpatients with recurrent motor fluctuations despite optimized PD medications (including levodopa) were enrolled.
- Participants initiated CSAI with a 1–2 mg bolus dose, followed by a 1 mg (0.2mL)/h infusion.
- CSAI was then titrated in 0.5–1 mg/h increments at clinic visits (1–10 days apart) to an optimal rate based on response and tolerability (maximum 8 mg/h).
- Other PD medications could be adjusted to manage dopaminergic side effects.
- Responders were defined as those with a ≥ 2 h improvement in OFF time from Baseline.

Results

- 99 patients were initiated on CSAI, 94 had post-baseline efficacy data and 85 completed the Titration Period. Demographics are shown in **Table 1**.
- Patients typically required 3 to 5 Titration visits (median=4 visits) for CSAI optimization. The median duration of the Titration Period was 30 days (**Figure 1**).
- 48 participants reduced concomitant PD medications during the Titration Period to manage dopaminergic AEs, with median time to first medication reduction of 9 days (range 2 to 44 days)

Patients were titrated to optimal CSAI rate at approximately weekly Titration visits before entering a 52-week Maintenance Period

Figure 1. InfusON Study Design



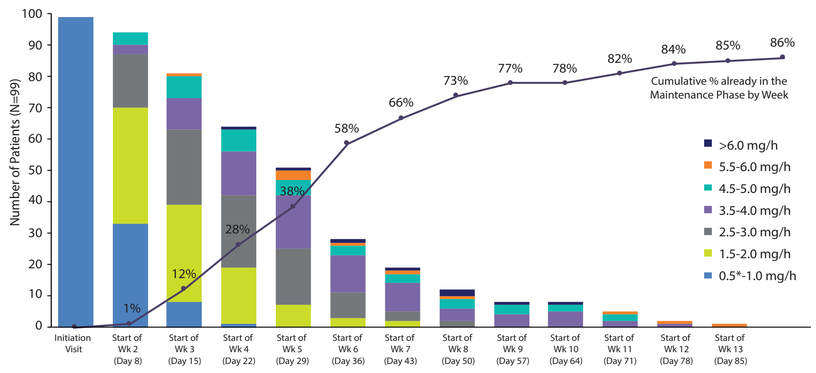
Initiation: 1–2 mg bolus (≥3h after last levodopa dose); then initiate 1 mg (0.2 mL)/h CSAI infusion (with up to 3 bolus doses/day). Titration and Optimization: Increase CSAI in 0.5–1.0 mg/h increments, over 3–5 visits, to best waking-day efficacy without intolerable AEs[Not to Exceed: 8 mg/h or 150 mg/day (w/boluses)]. PD med adjustment driven by dopaminergic side effects.

Table 1. Participant demographics

Category	N = 99
Age (y); mean ± SD	61.6 ± 9.41
Male, n (%)	69 (69.7)
PD duration (y); mean ± SD	10.0 ± 6.22
Duration of motor fluctuations (y); mean ± SD	5.3 ± 4.33
Motor states (h/ day); mean ± SD	n=94[a]
OFF time	6.6 ± 2.36
ON time without troublesome dyskinesia	9.3 ± 2.62
ON time with troublesome dyskinesia	0.5 ± 1.03
Levodopa products, n (%)	99 (100%)
Dopamine agonists[b], n (%)	79 (79.8%)
MAO-B Inhibitors, n (%)	33 (33.3%)
COMT Inhibitors, n (%)	20 (20.2%)
Amantadine, n (%)	31 (31.3%)

[a]Modified intent to treat population; [b]Not including Apokyn

Figure 2. Bars show CSAI doses for patients still in the Titration period at each week. Line shows the percentage of patients progressing to Maintenance per week.



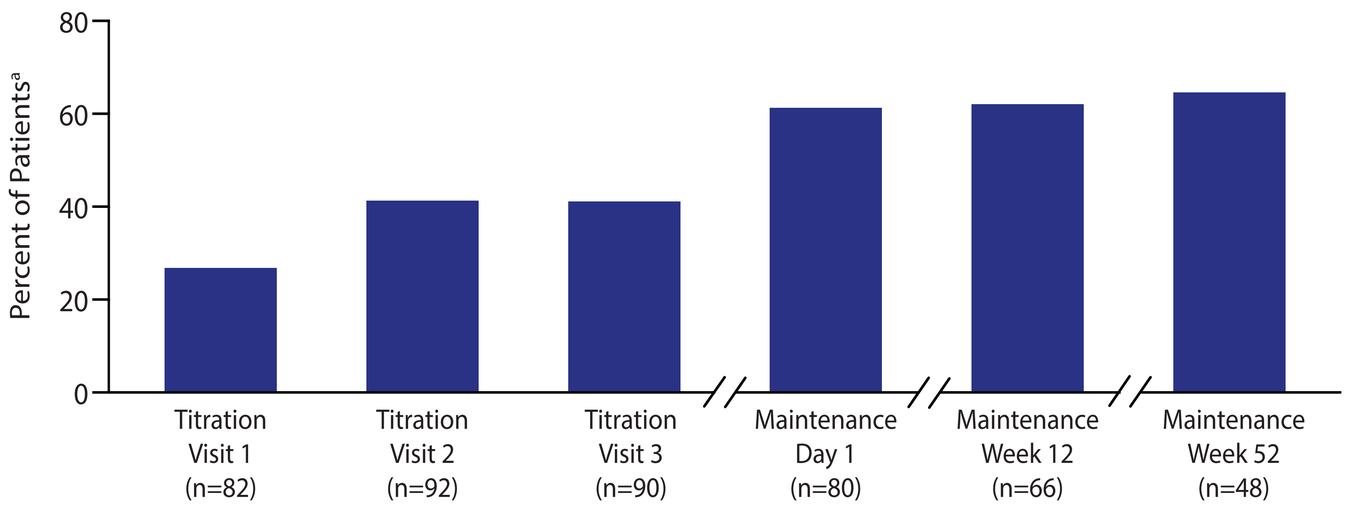
*Protocol updated after first 20 patients enrolled to increase initiation dose from 0.5 mg/h to 1.0 mg/h (per UK Summary of Product Characteristics)

Summary

- CSAI titration was well tolerated, with 85% of patients progressing to maintenance treatment (**Figure 2**).
- Improvement was rapid, with 27% of patients meeting response criteria at the initiation dose (**Figure 3**).
- Response rates increased with dose optimization (to 61%) and were sustained over the 52-week Maintenance period.
- Dopaminergic adverse events were managed by adjustment of concomitant PD medications.

Responder rates were 27% at the initiation dose, increased with CSAI optimization, and were sustained throughout the 52-week Maintenance Period.

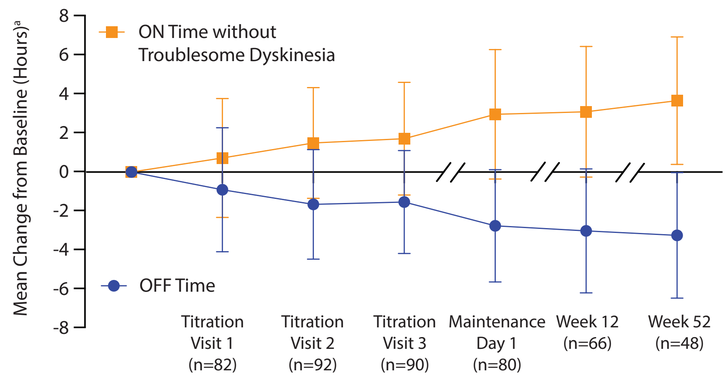
Figure 3. CSAI Responder rate (≥ 2h OFF time reduction)



[a]Percentages are based on the number of patients with diary data at each visit.

- Reduction in OFF time was noted already at the CSAI initiation dose, with 27% meeting response criteria before the first Titration Visit (**Figure 3**).
- Responder rates continued to improve with CSAI optimization, reaching 61% by the start of the Maintenance Period. Response rates were sustained through 52 weeks.
- Similarly, diary measures showed immediate improvement upon CSAI initiation, with reductions in OFF time and improvement in GOOD ON time that increased with CSAI optimization in the Titration Period and were sustained throughout the 52-week Maintenance Period (**Figure 4**).

Figure 4. ON time without troublesome dyskinesia increased, and OFF time decreased upon CSAI initiation and optimization, and were sustained through 52-week Maintenance.



[a]Error bars indicate standard deviation

- Adverse events during CSAI titration were mainly mild to moderate in severity, with infusion site nodules and/or erythema, dyskinesia, and nausea being the most commonly reported (**Table 2**).
  - Infusion site reactions were not severe, largely self-limiting, seldom led to discontinuation and did not impact efficacy.
  - Dyskinesia was managed by lowering concomitant PD medications (all patients had dyskinesia or history of dyskinesia at Baseline).
  - Nausea could be managed by slower titration; although patients received pretreatment with trimethobenzamide (Tigan), it is no longer available in the U.S. and its efficacy is not well-established. [Domperidone is not approved in the U.S.][2,3]

Table 2. Adverse events with onset during Titration Period

MedDRA Term	Incidence During Titration (%)	Severity (%)			Led to Discontinuation[a]
		Mild	Moderate	Severe	
Infusion site nodule	64	52	12	-	4
Dyskinesia	29	11	17	1	-
Nausea	24	19	5	-	3
Infusion site erythema	22	19	3	-	1
Dizziness	18	14	3	1	2
Somnolence	17	11	5	1	2
Infusion site bruising	15	15	-	-	-
Nasopharyngitis	12	10	2	-	-
Headache	11	10	1	-	-
Fall	10	8	2	-	-

[a]Discontinuation for some events may have occurred after the patient completed the Titration Period.

References

1) Jenner P, Falup-Pecurariu C, Leta V, et al. Neural Tansm (Vienna). 2023; 130(11):1337-1347.
2) Hauser RA, Isaacson S, Clinch T. Parkinsonism Relat Disord. 2014;20(11):1171-6.
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Disclosures

Stuart H. Isaacson, Peter LeWitt, Alberto J. Espay, Rajesh Pahwa, Pinky Agarwal, Holly A. Shill, Jennifer Hui, Khashayar Dashtipour, and Mark Lew were all investigators in the InfusON study and report fees for consultancy from US WorldMeds, LLC. Gianpiera Ceresoli-Borroni, Peibing Qin, Andrea Formella, and Mindy Grall are employed by Supernus Pharmaceuticals Inc.

For questions about these data, contact Supernus Medical Affairs at medinfo.supernus@apcerls.com