

## Rapid-acting dopaminergic therapy (RAD-T) and time to ON


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Is it time to consider earlier use in Parkinson's disease (PD)?


# Common treatment approaches to OFF episodes may not fully address patient needs<sup>1,2</sup>

In PD, OFF episodes are characterized by the reappearance and/or worsening of motor symptoms and/or nonmotor symptoms, and they can significantly erode quality of life.<sup>3</sup>


## OFF episodes are associated with difficulty:




Washing oneself<sup>4</sup>



Getting around the house<sup>4</sup>



Getting around in public<sup>4</sup>



Speaking/communicating<sup>4</sup>

Current OFF episode treatment approaches involve increasing baseline oral carbidopa/levodopa (CD/LD) dosage and frequency, followed by adding ON-extendeder therapy.<sup>1,2</sup>

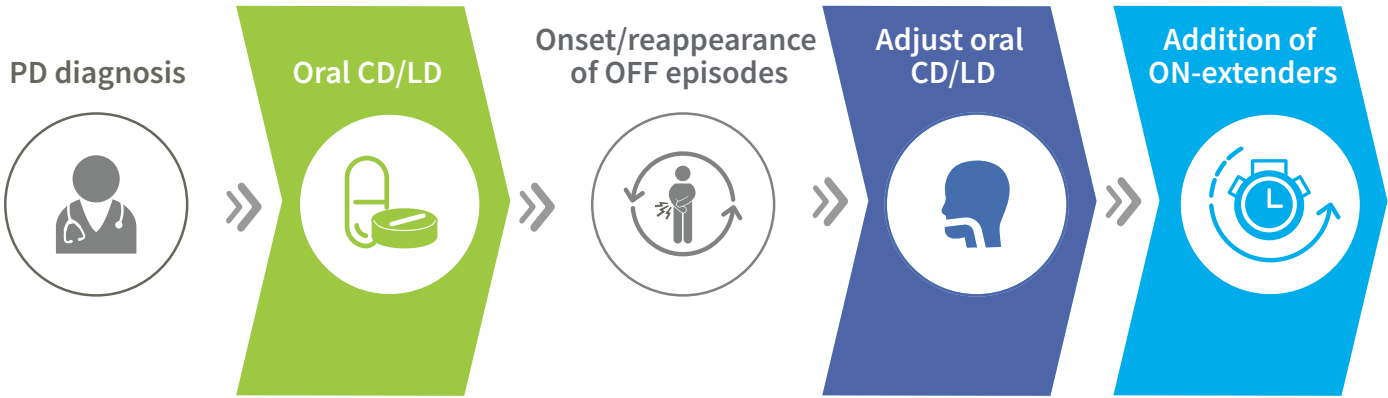
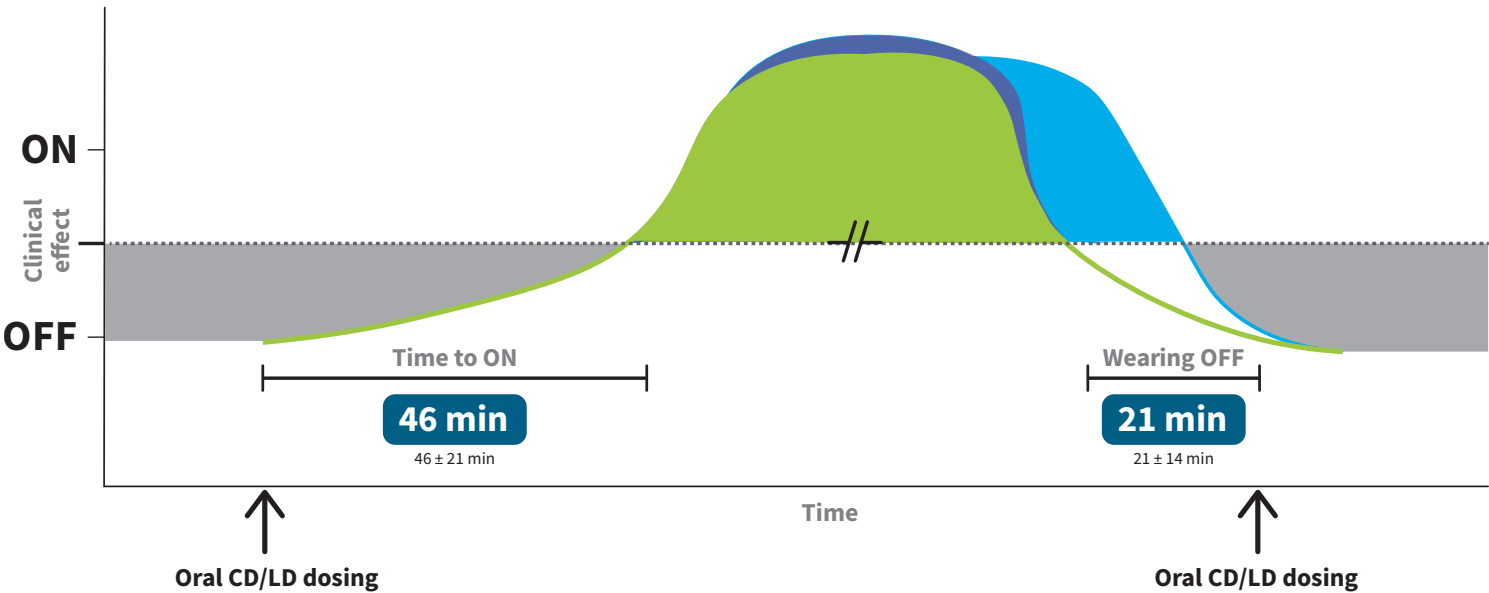
## Challenges that can impact the optimal delivery of CD/LD, which may further delay ON time<sup>5-7</sup>:

- General swallowing problems
- Competition with amino acids
- Gastroparesis (delayed emptying of the stomach)

Gastroparesis (delayed emptying of the stomach) can lead to variable absorption of CD/LD, which may further delay ON time<sup>7</sup>

# Time to ON can account for 2X more daily OFF time than wearing OFFs<sup>8</sup>

## OFF EPISODES MAY OCCUR WITH EACH CD/LD DOSE THROUGHOUT THE DAY<sup>5,6,8\*</sup>

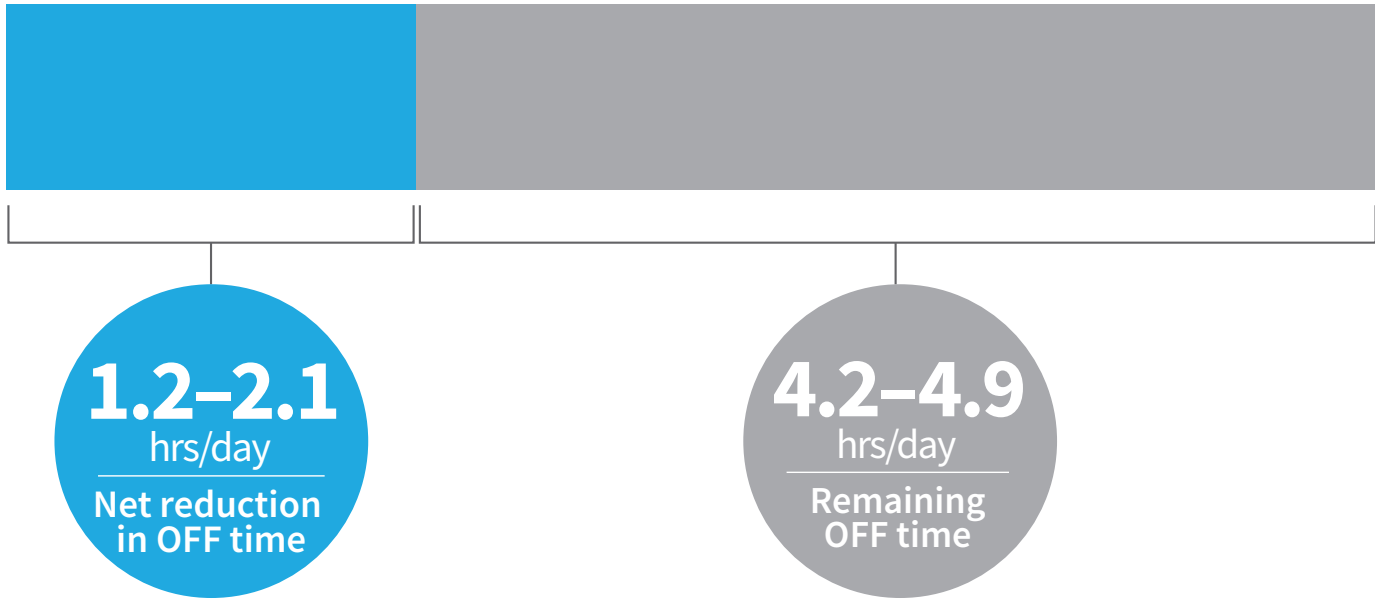


## CURRENT TREATMENT APPROACHES<sup>1,2,9</sup>

\*Adapted from a daily study of 20 patients with advanced PD receiving levodopa (mean total daily dose of 821 mg, 5–9 divided daily doses).<sup>8</sup> Graphic is not to scale.

Despite treatment with ON-extenders,\* patients may still experience up to 5 hours of OFF time daily<sup>10-19</sup>

IN PLACEBO-CONTROLLED TRIALS, THE USE OF ON-EXTENDERS RESULTED IN A NET REDUCTION OF OFF TIME RANGING BETWEEN 1.2-2.1 HOURS/DAY AND REMAINING OFF TIME RANGED FROM 4.2-4.9 HOURS/DAY<sup>10-19</sup>



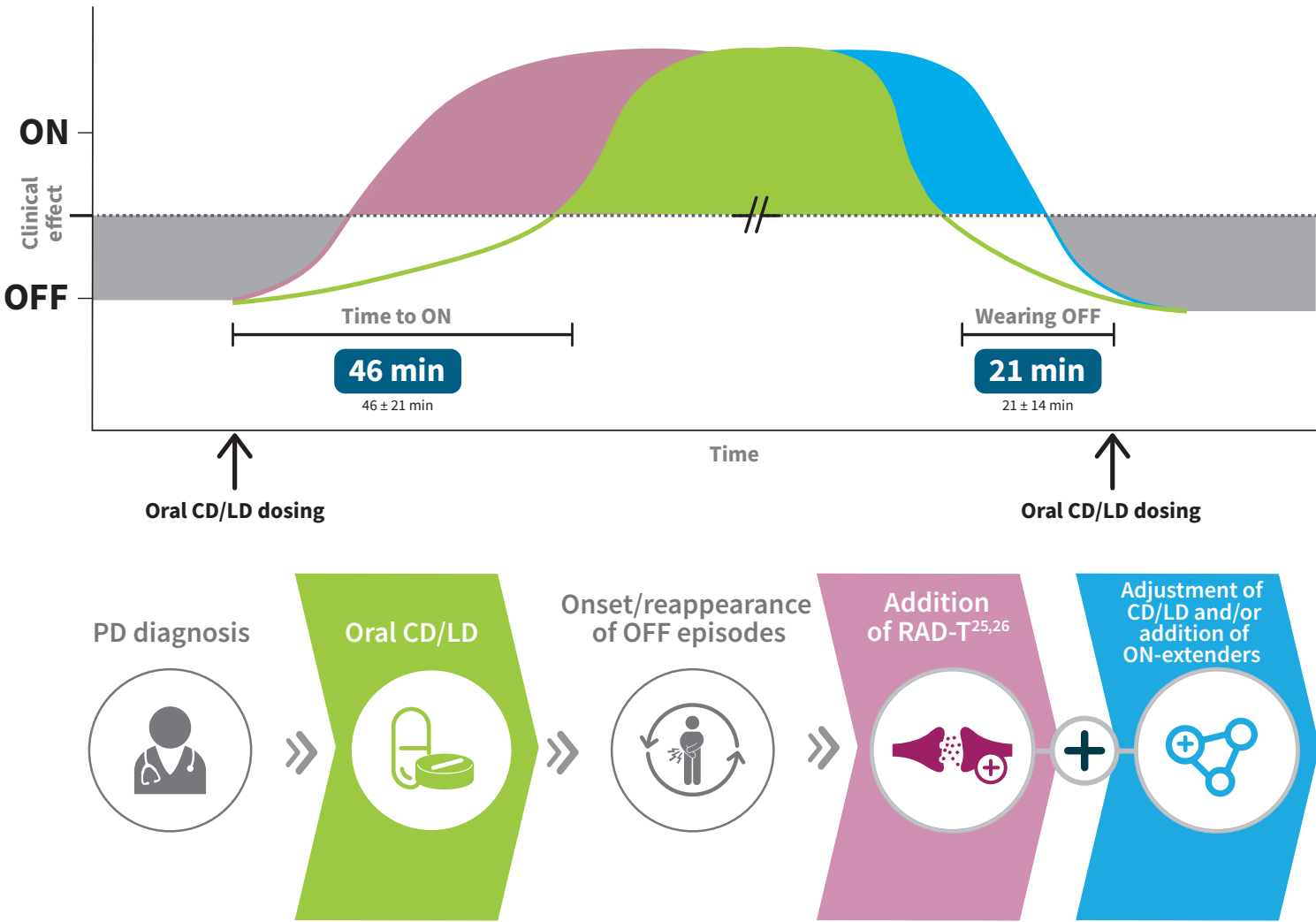
\*Select ON-extendors include a dopamine agonist, COMT (catechol-O-methyltransferase) inhibitor, MAO-B (monoamine oxidase-B) inhibitor, and adenosine A<sub>2A</sub> receptor antagonist. This is not an inclusive list of all adjunctive PD medications.<sup>10-19</sup>

Is rapid-acting dopaminergic therapy (RAD-T) a solution to address continued gaps in time to ON?

Is it time to consider earlier use of RAD-T for OFF episodes?

RAD-Ts are approved for the intermittent treatment of OFF episodes.<sup>20-23</sup> The versatility of RAD-T makes it a complementary partner to current treatment approaches at any time after the onset of OFF episodes.<sup>20-24</sup>

A POTENTIAL APPROACH UTILIZING RAD-T FOR THE TREATMENT OF OFF EPISODES<sup>8,21-23\*</sup>



\*Adapted from a daily study of 20 patients with advanced PD receiving levodopa (mean total daily dose of 821 mg, 5-9 divided daily doses).<sup>8</sup> Graphic is not to scale.

It's time to consider earlier use of RAD-T for OFF episodes. The versatility of RAD-T makes it a complementary partner to current treatment approaches at any time after the onset of OFF episodes<sup>20-24</sup>

**References:** 1. Armstrong MJ, Okun MS. Diagnosis and treatment of Parkinson disease: a review. *JAMA*. 2020;323(6):548-560. 2. Fox SH, Katzenschlager R, Lim S-Y, et al; Movement Disorder Society Evidence-Based Committee. International Parkinson and Movement Disorder Society evidence-based medicine review: update on treatments for the motor symptoms of Parkinson's disease. *Mov Disord*. 2018;33(8):1248-1266. 3. Chou KL, Stacy M, Simuni T, et al. The spectrum of "off" in Parkinson's disease: what have we learned over 40 years? *Parkinsonism Relat Disord*. 2018;51:9-16. 4. Thach A, Jones E, Pappert E, Pike J, Wright J, Gillespie A. Real-world assessment of the impact of "OFF" episodes on health-related quality of life among patients with Parkinson's disease in the United States. *BMC Neurol*. 2021;21(46):1-12. 5. Stocchi F, Coletti C, Bonassi S, Radicati FG, Vacca L. Early-morning OFF and levodopa dose failures in patients with Parkinson's disease attending a routine clinical appointment using Time-to-ON Questionnaire. *Eur J Neurol*. 2019;26(5):821-826. 6. Thanvi BR, Lo TCN. Long term motor complications of levodopa: clinical features, mechanisms, and management strategies. *Postgrad Med J*. 2004;80(946):452-458. 7. Müller T, Erdmann C, Bremen D, et al. Impact of gastric emptying on levodopa pharmacokinetics in Parkinson's disease patients. *Clin Neuropharmacol*. 2006;29(2):61-67. 8. Merims D, Djaldetti R, Melamed E. Waiting for ON: a major problem in patients with Parkinson disease and ON/OFF motor fluctuations. *Clin Neuropharmacol*. 2003;26(4):196-198. 9. Rao SS, Hoffman LA, Shakil A. Parkinson's disease: diagnosis and treatment. *Am Fam Physician*. 2006;74(12):2046-2054. 10. Ferreira JJ, Lees A, Rocha J-F, Poewe W, Rascol O, Soares-da-Silva P; Bi-Park 1 Investigators. Opicapone as an adjunct to levodopa in patients with Parkinson's disease and end-of-dose motor fluctuations: a randomised, double-blind, controlled trial. *Lancet Neurol*. 2016;15(2):154-165. 11. Ongentys. Prescribing information. Neurocrine Biosciences, Inc; April 2020. 12. Rinne UK, Larsen JP, Siden A, Worm-Petersen J; Nomecom Study Group. Entacapone enhances the response to levodopa in parkinsonian patients with motor fluctuations. *Neurology*. 1998;51(5):1309-1314. 13. Comtan. Prescribing information. Orion Pharma; September 2010. 14. Pahwa R, Stacy MA, Factor SA, et al; EASE-PD Adjunct Study Investigators. Ropinirole 24-hour prolonged release: randomized, controlled study in advanced Parkinson disease. *Neurology*. 2007;68(14):1108-1115. 15. Requip XL. Prescribing information. GlaxoSmithKline; March 2017. 16. LeWitt PA, Guttman M, Tetrad JW, et al; 6002-US-005 Study Group. Adenosine A<sub>2A</sub> receptor antagonist istradefylline (KW-6002) reduces "off" time in Parkinson's disease: a double-blind, randomized, multicenter clinical trial (6002-US-005). *Ann Neurol*. 2008;63(3):295-302. 17. Nourianz. Prescribing information. Kyowa Kirin, Inc; May 2020. 18. Rascol O, Brooks DJ, Melamed E, et al; LARGO Study Group. Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomised, double-blind, parallel-group trial. *Lancet*. 2005;365(9463):947-954. 19. Azilect. Prescribing information. TEVA Neuroscience, Inc; May 2014. 20. Olanow CW, Factor SA, Espay AJ, et al; CTH-300 Study Investigators. Apomorphine sublingual film for off episodes in Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Neurol*. 2020;19(2):135-144. 21. Inbrija. Prescribing information. Acorda Therapeutics, Inc; August 2020. 22. Apokyn. Prescribing information. US WorldMeds, LLC; April 2020. 23. Kynmobi. Prescribing information. Sunovion Pharmaceuticals Inc; August 2021. 24. Olanow CW, Poewe W, Rascol O, Stocchi F. On-demand therapy for OFF episodes in Parkinson's disease. *Mov Disord*. 2021;36(10):2244-2253. 25. Hui JS, Fox SH, Neeson W, et al; CTH-300 Study Investigators. Open-label titration of apomorphine sublingual film in patients with Parkinson's disease and "OFF" episodes. *Parkinsonism Relat Disord*. 2020;79:110-116. 26. Parkinson's Foundation. Managing PD mid-stride: a treatment guide to Parkinson's disease. 2018. Accessed February 14, 2022. <https://www.parkinson.org/sites/default/files/attachments/MidStride.pdf>.