The role of Duopa in the management of Parkinson's disease

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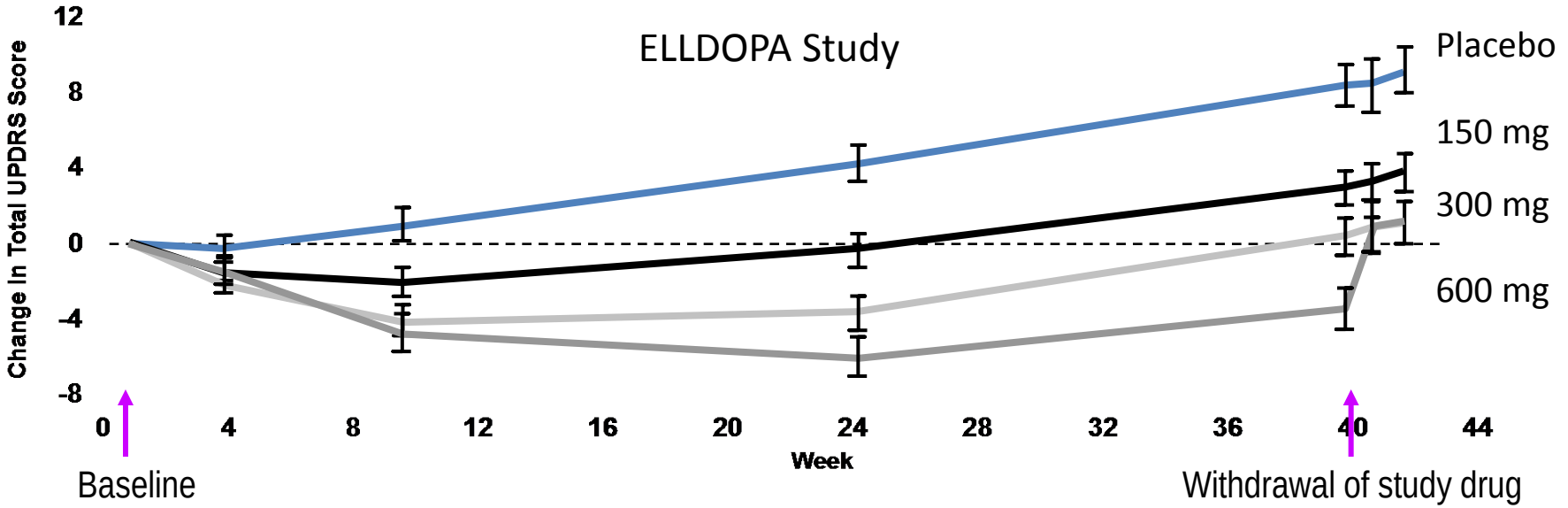
Objectives

- **Distinguish** the Duopa delivery system from other therapies in PD.
- **Describe** the indications for Duopa.
- **Select** appropriate patients for this therapy.
- **Discuss** the potential risks and benefits with those patients that might be candidates for the therapy.

Disclosures

- Dr. Rodriguez has received research support from Solvay and Abbvie over the last 8 years to support the clinical development of the intestinal carbidopa/levodopa suspension and has served as an advisor, consultant and speaker for Abbvie.

Levodopa Reduces Symptoms in Early PD but is Associated with Motor Complications

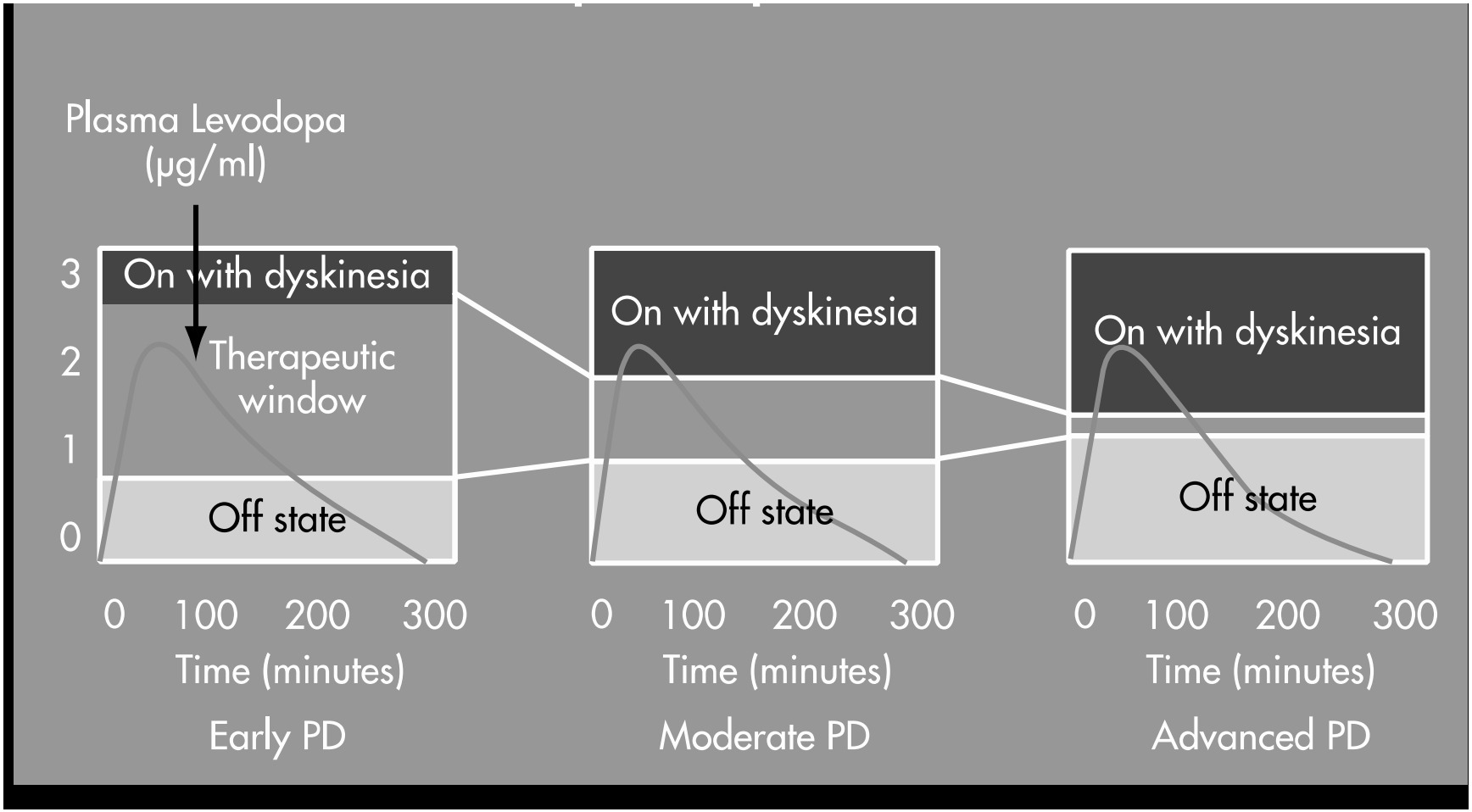


		Levodopa		
	Placebo (N = 90)	150 mg/day (N = 92)	300 mg/day (N = 88)	600 mg/day (N = 91)
Adverse Motor Event	**Number (percent)**			**P-value**
Dyskinesia	**3 (3.3)**	**3 (3.3)**	**2 (2.3)**	**15 (16.5)**	**< 0.001**
Wearing off	**12 (13.3)**	**15 (16.3)**	**16 (18.2)**	**27 (29.7)**	**0.06**

UPDRS = Unified Parkinson's Disease Rating Scale

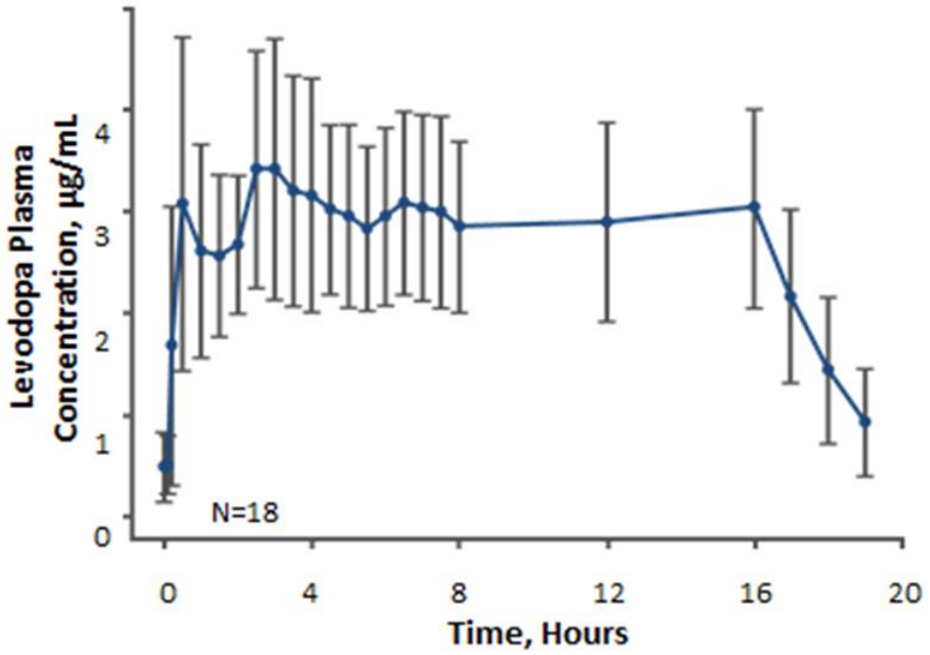
Parkinson Study Group. *N Engl J Med*. 2004;351:2498-2508.

Progression of PD



DUOPA: Pharmacokinetics

Plasma Concentrations vs Time Profile of Levodopa With 16-Hour Infusion of Duopa[1,2,*,†]



Study Design[2]:

- Multicenter, multiple-dose, open-label study in 18 patients with advanced PD
- Individually optimized dosing was delivered over a 16-hour period, administered as a Morning Dose followed by a continuous infusion
- Intermittent Extra Doses were allowed but discouraged on sampling days
- Patients received standardized, low-protein meals during the assessment days

*All patients had been on Duopa therapy for ≥30 days **and remained on their individualized Duopa dose.[1]**

†Mean ± standard deviation.[1]

1. Duopa [package insert]. North Chicago, IL: AbbVie Inc. 2. Nyholm D, et al. *AAPS J.* 2013;15:316-323.

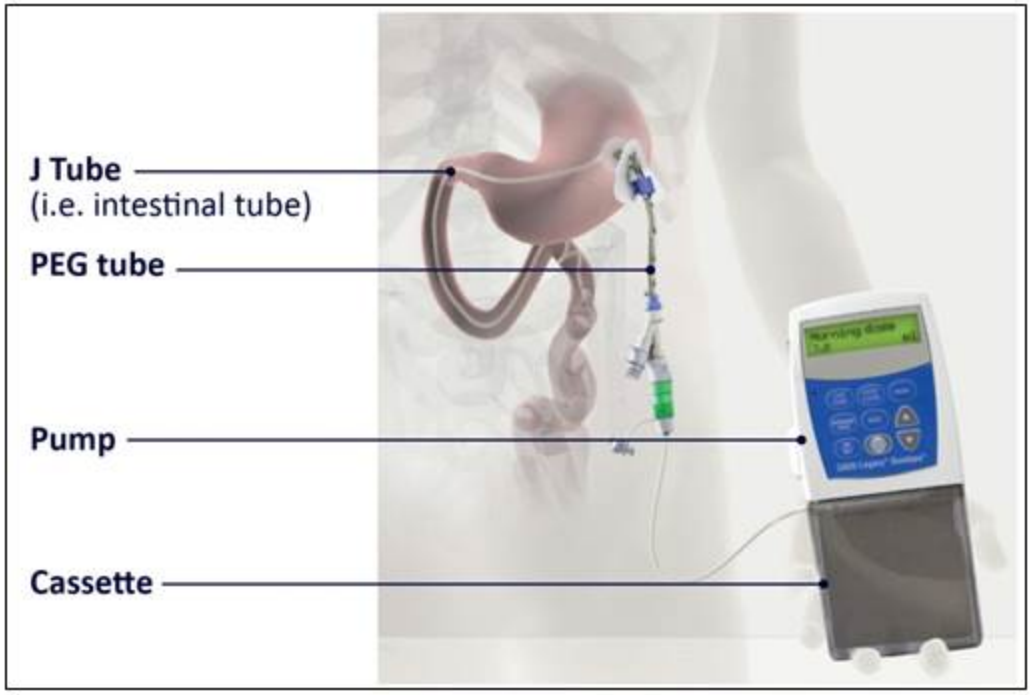
DUOPA Prescribing Information, available at www.rxabbvie.com.

DUOPA: Indication

DUOPA is indicated for the treatment of motor fluctuations in patients with advanced Parkinson's disease

DUOPA Prescribing Information, available at www.rxabbvie.com.

DUOPA System



The DUOPA system includes the following components:

- Single-use cassette containing 4.63 mg carbidopa (as 5 mg of the monohydrate) and 20 mg levodopa per ml of enteral suspension. Each cassette contains approximately 100 mL of suspension.
- Pump: CADD-Legacy® 1400 ambulatory infusion pump
- PEG tube
- Jejunal extension tube

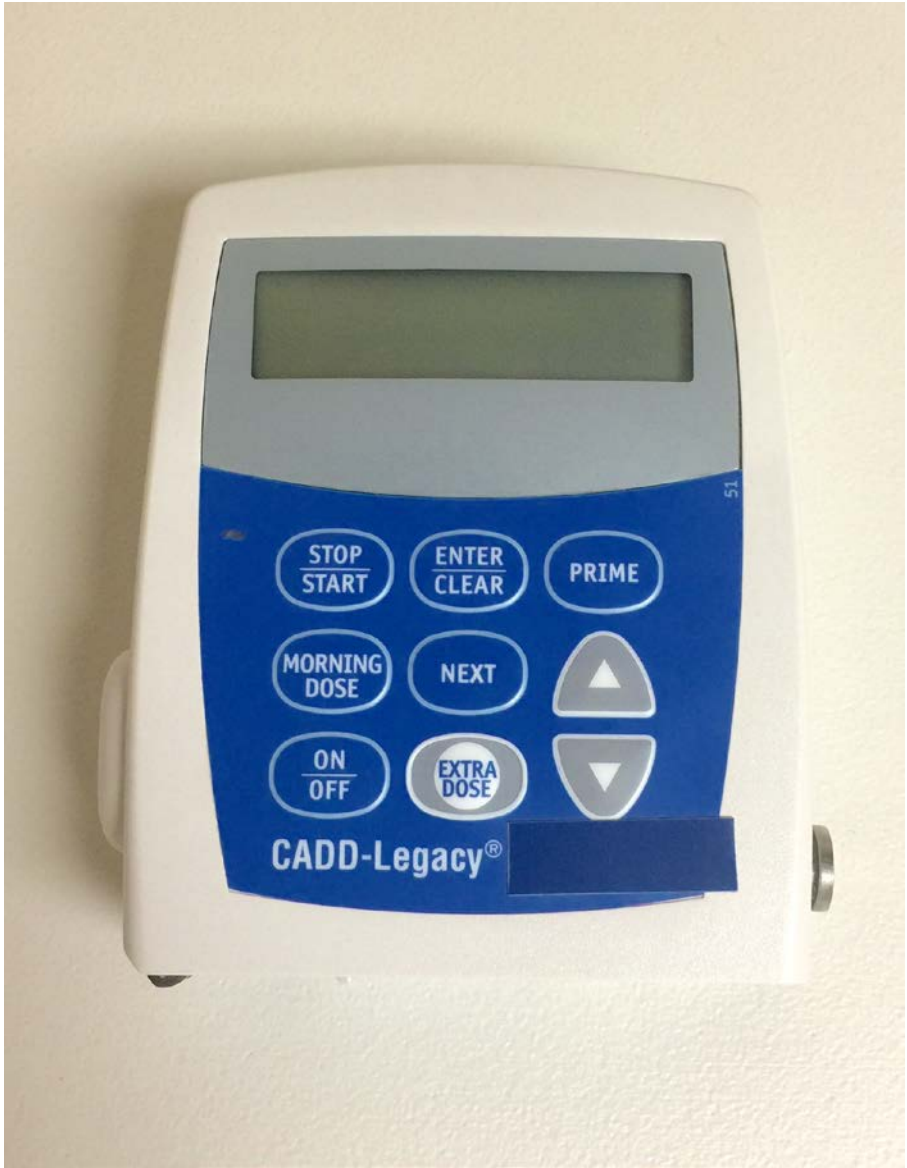
- Long term administration of DUOPA requires placement of a PEG-J outer transabdominal tube and inner jejunal tube by percutaneous endoscopic gastrostomy
- DUOPA is infused into the small intestine via PEG-J from medication cassette reservoirs that are specifically designed to be connected to the CADD®-Legacy 1400 pump

DUOPA Prescribing Information, available at www.rxabbvie.com.

Pump


STOP START
ENTER CLEAR
PRIME
MORNING DOSE
NEXT
ON OFF
EXTRA DOSE
CADD-Legacy®

Pump


STOP
START
ENTER
CLEAR
PRIME
MORNING
DOSE
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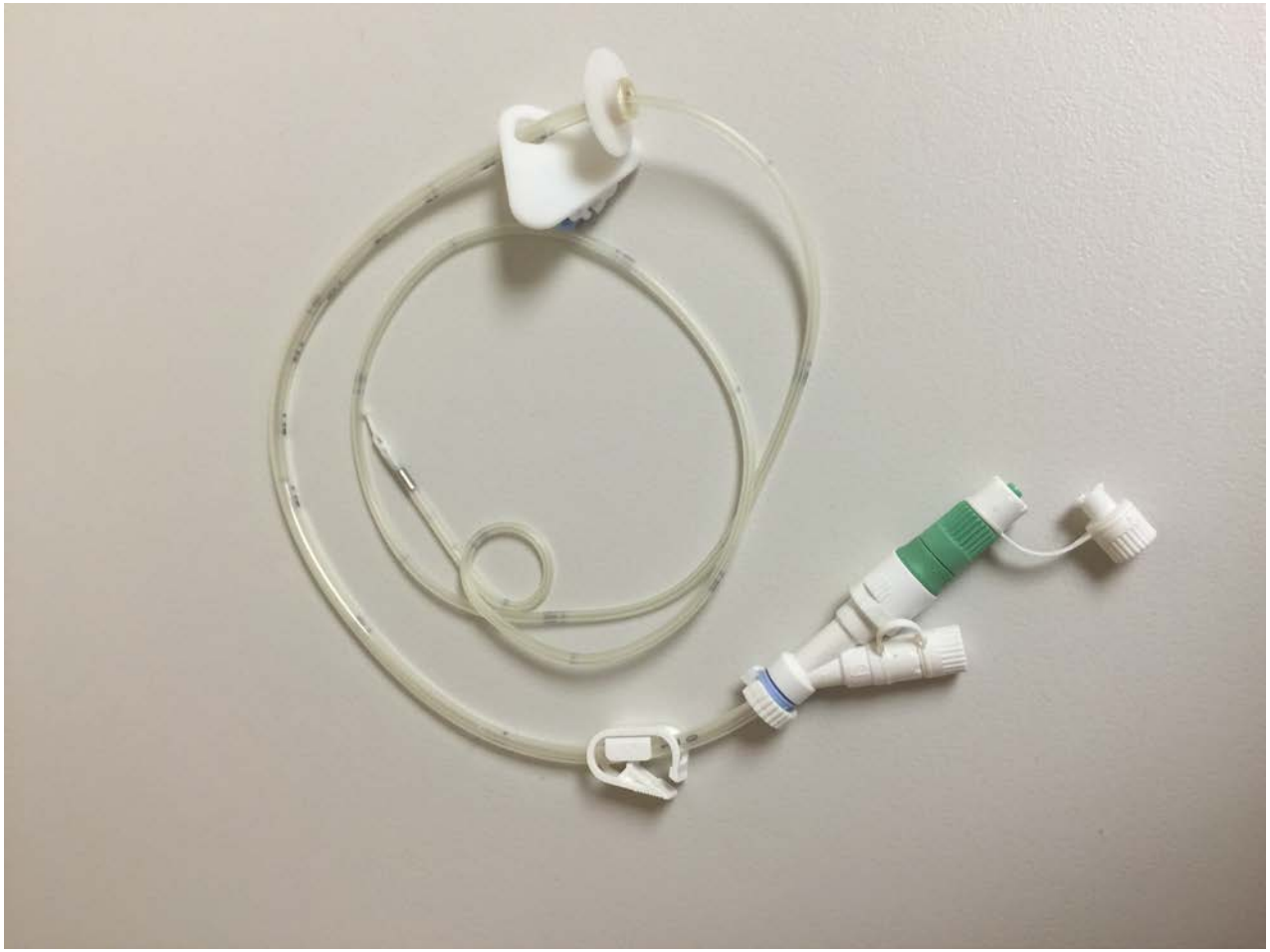
ON
OFF
EXTRA
DOSE
CADD-Legacy®

Cassette

Tubing



DUOPA: Pivotal Study Overview

- 12-week, randomized, double blind, double dummy, active-controlled study of DUOPA plus placebo capsules vs oral immediate-release carbidopa/levodopa (CL-IR) plus placebo gel
- All subjects had PEG-J placement

Clinical Outcome Measure
Mean change from baseline to Week 12 in the total daily mean "Off" time, based on a Parkinson's disease diary[a]

[a] The "Off" time was normalized to a 16-hour awake period, based on a person's typical waking day and the daily infusion of 16 hours

***Lancet Neurol* 2014; 13: 141–49**

Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study

C Warren Olanow, Karl Kieburtz, Per Odin, Alberto J Espay, David G Standaert, Hubert H Fernandez, Arvydas Vanagunas, Ahmed A Othman, Katherine L Widnell, Weining Z Robieson, Yili Pritchett, Krai Chatamra, Janet Benesh, Robert A Lenz, Angelo Antonini, for the LCIG Horizon Study Group

Lancet Neurol 2014; 13: 141–49

	Levodopa-carbidopa intestinal gel (n=37)	Immediate-release oral levodopa-carbidopa (n=34)
Age, years	63·7 (9·5)	65·1 (6·8)
Sex		
Men	24 (65%)	22 (65%)
Women	13 (35%)	12 (35%)
Ethnic group, white	35 (95%)	31 (91%)
Duration of Parkinson's disease, years	10·0 (4·6)	11·8 (5·6)
Off-time, h per day*	6·3 (1·7)	7·0 (2·1)
On-time without dyskinesia, h per day*	6·3 (2·7)	5·6 (3·2)
On-time with non-troublesome dyskinesia, h per day*	2·4 (1·8)	2·2 (2·2)
On-time without troublesome dyskinesia, h per day†	8·7 (2·0)	7·8 (2·5)
On-time with troublesome dyskinesia, h per day*	1·0 (1·6)	1·2 (1·7)
Unified Parkinson's Disease Rating Scale*		
Part I	1·8 (1·7)	1·8 (1·8)
Part II	11·6 (6·9)	11·8 (7·0)
Part III	18·1 (9·9)	22·5 (11·7)
Overall	31·5 (15·6)	35·8 (18·9)
Parkinson Disease Questionnaire-39*	35·1 (18·0)	38·6 (17·9)
Mini-Mental State Examination	28·7 (1·4)	28·9 (1·4)
Daily levodopa dose, mg	1005·4 (373·6)	1123·5 (477·9)
Antiparkinsonian medication use		
Dopamine agonist	22 (59%)	26 (76%)
COMT inhibitor	18 (49%)	15 (44%)
MAO-B inhibitor	15 (41%)	6 (18%)

Data are mean (SD) or n (%). COMT=catechol-O-methyl transferase. MAO-B=monoamine oxidase B. *36 patients in the intestinal gel group and 33 patients in the immediate-release group were included in the full-analysis set. †On-time without troublesome dyskinesia equals on-time without dyskinesia plus on-time with non-troublesome dyskinesia.

Table 1: **Baseline characteristics**

	Levodopa-carbidopa intestinal gel (n=35)	Immediate-release oral levodopa-carbidopa (n=31)	Treatment difference (95% CI)	p value
Primary efficacy outcome				
Off-time, h per day	−4·04 (0·65)	−2·14 (0·66)	−1·91 (−3·05 to −0·76)	0·0015
Secondary efficacy outcomes				
On-time without troublesome dyskinesia, h per day*	4·11 (0·75)	2·24 (0·76)	1·86 (0·56 to 3·17)	0·0059
On-time without dyskinesia, h per day†	3·37 (1·04)	1·09 (1·05)	2·28 (0·47 to 4·09)	0·0142
On-time with non-troublesome dyskinesia, h per day†	0·81 (0·86)	1·54 (0·86)	−0·73 (−2·22 to 0·76)	0·3294
On-time with troublesome dyskinesia, h per day†	−0·11 (0·52)	−0·03 (0·52)	−0·08 (−0·98 to 0·82)	0·8574
PDQ-39 summary index	−10·9 (3·3)	−3·9 (3·2)	−7·0 (−12·6 to −1·4)	0·0155
Mean CGI-I score at final assessment‡	2·3 (0·4)	3·0 (0·4)	−0·7 (−1·4 to −0·1)	0·0258
UPDRS part II§	−1·8 (1·3)	1·3 (1·3)	−3·0 (−5·3 to −0·8)	0·0086
UPDRS part III§	−1·5 (2·4)	−2·9 (2·4)	1·4 (−2·8 to 5·6)	0·5020
EQ-5D	0·05 (0·04)	−0·02 (0·04)	0·07 (−0·01 to 0·15)	0·0670
Zarit Burden Interview	−2·8 (3·7)	1·7 (3·3)	−4·5 (−10·7 to 1·7)	0·1501
Levodopa total daily dose, mg	91·7 (96·6)	249·7 (94·9)	−158·0 (−324·5 to 8·5)	0·0625
Overall mean (SD) levodopa rescue dose, mg	139·8 (20·3)	180·6 (21·9)	−40·8 (−100·4 to 18·8)	0·1762

Data are the least squares mean change from baseline to week 12 (SE) unless otherwise stated. PDQ=Parkinson Disease Questionnaire. CGI-I=Clinical Global Impression–Improvement. UPDRS=Unified Parkinson's Disease Rating Scale. EQ-5D=EuroQual quality of life-5 Dimensions. *On-time without troublesome dyskinesia equals on-time without dyskinesia plus on-time with non-troublesome dyskinesia. †Measure not part of hierarchical analysis; ‡For CGI-I, 1 is very much improved, 2 is much improved, 3 is minimally improved, 4 is no change, 5 is minimally worse, 6 is much worse, and 7 is very much worse. §UPDRS was completed in the on-state.

Table 2: **Treatment efficacy**

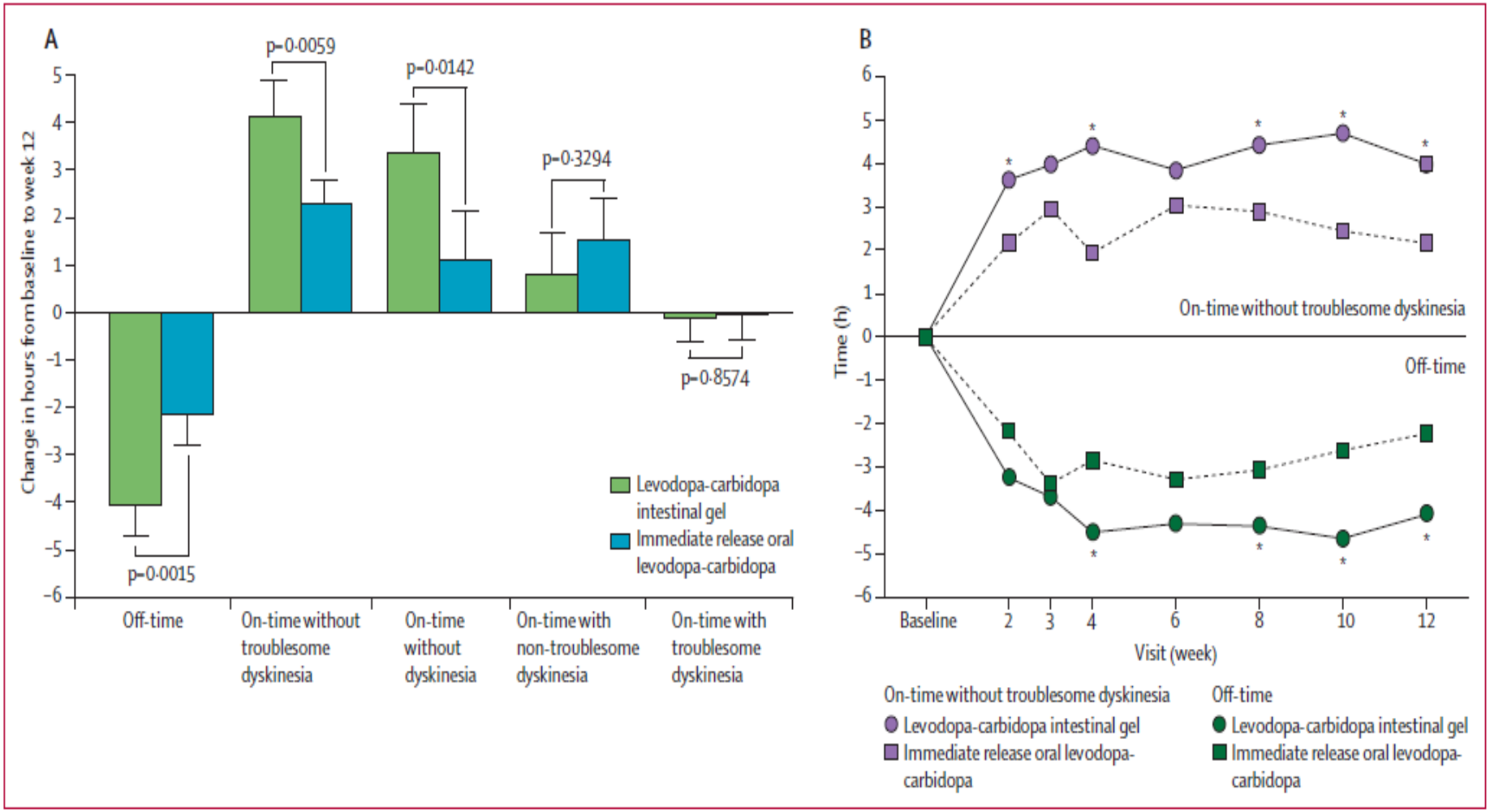


Figure 2: **Diary measures**

(A) Home diary results: change between baseline and week 12 in various Parkinson's disease motor states. (B) Home diary results: Parkinson's disease motor states at each visit. *p<0·05. For each variable, data shown are the least squares means (error bars) from the symptom diary for the 3 consecutive days before the clinic visit, normalised to a 16 h waking day. On-time without troublesome dyskinesia equals on-time without dyskinesia plus on-time with non-troublesome dyskinesia. Data for 35 patients in the levodopa-carbidopa intestinal gel group and 31 patients in the immediate-release oral levodopa-carbidopa group.

DUOPA: Pivotal Study PD Symptom Diary Analysis

Change From Baseline to Week 12 in "Off" time and in "On" Time Without Troublesome Dyskinesia in Patients With Advanced Parkinson's Disease

Treatment Group	Baseline (hours)	LS Mean Change From Baseline at Week 12 (hours)[a]
"Off" Time		
DUOPA	**6.3**	**-4.0[b]**
Oral CL-IR	**6.9**	**-2.1**
"On" Time Without Troublesome Dyskinesia		
DUOPA	**8.7**	**4.1[b]**
Oral CL-IR	**8.0**	**2.2**

Abbreviations: CL-IR, carbidopa/levodopa immediate-release; LS, least square
[a] LS mean change from baseline based on Analysis of Covariance (ANCOVA).
[b] Statistically significant.

The mean score decrease (improvement) in "Off" time from baseline to Week 12 for DUOPA was significantly greater than for oral immediate-release carbidopa/levodopa (CL-IR; *P*=0.0015). The mean score increase (improvement) in "On" time without troublesome dyskinesia was also significantly greater for DUOPA than for CL-IR (*P*=0.0059).

DUOPA Prescribing Information, available at www.rxabbvie.com.

DUOPA: Pivotal Study Adverse Reactions*

Adverse Reaction	DUOPA (n=37) %	Oral immediate-release levodopa-carbidopa (n=34) %
Complication of device insertion	57	44
Nausea	30	21
Constipation	22	21
Incision site erythema	19	21
Dyskinesia	14	12
Depression	11	3
Post procedural discharge	11	9
Peripheral edema	8	0
Hypertension	8	0
Upper respiratory tract infection	8	0
Oropharyngeal pain	8	0
Atelectasis	8	0
Confusional state	8	3

*incidence of adverse reactions occurring in the DUOPA-treated group (requiring at least 2 patients in this group) in Study 1 when the incidence was numerically greater than that for oral immediate-release carbidopa-levodopa.

DUOPA Prescribing Information, available at www.rxabbvie.com.

DUOPA: Pivotal Study Adverse Reactions, Continued*

Adverse Reaction	DUOPA (n=37) %	Oral immediate-release levodopa-carbidopa (n=34 %
Anxiety	8	3
Dizziness	8	6
Hiatal hernia	8	6
Postoperative ileus	5	0
Sleep disorder	5	0
Pyrexia	5	0
Excessive granulation tissue	5	0
Rash	5	0
Bacteriuria	5	0
White blood cells urine positive	5	0
Hallucinations	5	3
Psychotic disorder	5	3
Diarrhea	5	3
Dyspepsia	5	3

*incidence of adverse reactions occurring in the DUOPA-treated group (requiring at least 2 patients in this group) in Study 1 when the incidence was numerically greater than that for oral immediate-release carbidopa-levodopa.

DUOPA Prescribing Information, available at www.rxabbvie.com.

Long Term Efficacy

- In the Phase 3 Clinical Program, the safety and efficacy of LCIG was evaluated in a 52-week open-label extension study of the 12-week, randomized pivotal trial and a 54-week, open-label safety study.

Fernandez HH, Standaert DG, Hauser RA, et al. Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: final 12-month open-label results. *Mov Disord*. 2015;30(4):500-509.

Long Term Efficacy

- In the 52-week, open-label extension study, subjects who were previously LCIG-naïve reported significant improvements in “Off” time and “On” time without troublesome dyskinesias.
- Subjects previously receiving LCIG reported significant improvements in “On” time without troublesome dyskinesia and sustained “Off” time duration compared with baseline (considered to be the end of the double-blind trial).

Fernandez HH, Standaert DG, Hauser RA, et al. Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: final 12-month open-label results. *Mov Disord*. 2015;30(4):500-509.

Long Term Efficacy

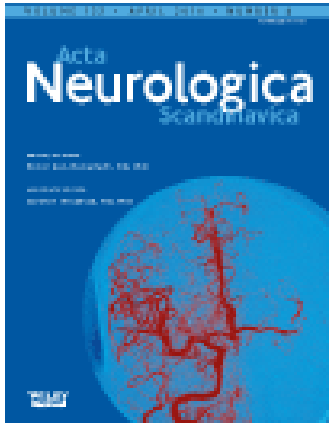
- Additionally significant improvements from baseline were reported for both groups for Unified Parkinson's Disease Rating Scale (UPDRS) IV scores, UPDRS dyskinesia items, and Clinical Global Impression Improvement (CGI-I) scores in subjects previously receiving LCIG only.
- No significant changes from the end of the double-blind trial were reported for the total UPDRS, UPDRS I-III subscores, quality of life (QoL) measures, or caregiver burden for either group.

Fernandez HH, Standaert DG, Hauser RA, et al. Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: final 12-month open-label results. *Mov Disord*. 2015;30(4):500-509.

Duopa and dyskinesias

Improvement of dyskinesias with l-dopa infusion in advanced Parkinson's disease

The mean time spent in *on with troublesome dyskinesia* per day after 6 months of LCIG therapy decreased by 47% ($P < 0.05$).



Timpka J, Fox T, Fox K, Honig H, Odin P, Martinez-Martin P, Antonini A, Ray Chaudhuri K. Improvement of dyskinesias with l-dopa infusion in advanced Parkinson's disease. Acta Neurol Scand

Duopa and dyskinesias

Effect of levodopa-carbidopa intestinal gel on dyskinesia in advanced Parkinson's disease patients.

Antonini A[1], Fung VS[2], Boyd JT[3], Slevin JT[4], Hall C[5], Chatamra K[5], Eaton S[5], Benesh JA[5].

…levodopa-carbidopa intestinal gel treatment resulted in a reduction from baseline in "on" time with troublesome dyskinesia (mean [standard deviation] hours: baseline = 3.1 [1.7], change from baseline to final = -1.8 [1.8], P = .014), increase in "on" time without troublesome dyskinesia (baseline = 7.4 [2.2], change = 4.4 [3.6], P = .004), and decrease in "off" time (baseline = 5.5 [1.3], change = -2.7 [2.8], P = .015).

Mov Disord. 2016 Jan 28. doi: 10.1002/mds.26528.

Suggested Patient Selection

- Patient Characteristics:
  - Diagnosis of Idiopathic Parkinson's disease according to the UKPD Brain Bank criteria.
  - Documented response to levodopa, with at least a 30% improvement in the UPDRS part 3 after a supramaximal dosage of levodopa. A supramaximal dose is considered to be 150% of the regular dosage of levodopa the patient takes at home given at least 12 hours apart from the last regular dose.
  - MMSE score of 24 or more.
  - Patient is able to recognize "on" and "off" states.

Suggested patient selection

- Must have at least 2 hours of “off time” despite optimization of medical therapy. Optimization of medical therapy, for this purpose, is defined as the patient having been tried on the medications in #6 in appropriate dosages to observe a response and the patient continues to perceive that the quality of life is still affected by the persistent motor fluctuations. Minimum dosing frequency for levodopa should be at least 5 times/day.
- Patient must have been tried on at least one agent in all the following classes of therapies with documentation of lack of efficacy and/or poor tolerability/side effects:
  - Dopamine agonists (pramipexole, ropinirole, rotigotine)
  - COMT inhibitors (entacapone, tolcapone)
  - Oral levodopa formulations (any carbidopa/levodopa in any formulation)
  - Amantadine
  - MAOI’s (selegiline, rasagiline)

Suggested patient selection

- Patient must fully understand the goals of the therapy and must be able to provide consent. In particular, patient must understand that CLES is not a cure for PD, and the main objective of therapy is to decrease “off time” periods and increase “on time without troublesome dyskinesias”.
- Patient must be considered a good candidate for PEG J placement in the judgement of the GI service. Contraindications include but are not limited to the following situations:
  - Known or suspected intestinal obstruction
  - Serious coagulation disorders
  - Sepsis
  - Active peritonitis

Suggested patient selection

- Relative contraindications for PEG J include, but are not limited to:
  - Ascites and neoplastic, inflammatory and infiltrative disease of the gastric and abdominal walls.
- Patient or caregiver, in the opinion of the referring physician, should be able to perform the required manipulation of the medication pump.
- Patient must take home a sample pump for at least three days, pretending the device is in place, to make sure this is something that he/she will be able to accommodate in his/her daily routine.

Suggested patient selection

- Patient must understand that those symptoms that do not improve with levodopa are not expected to improve with CLES.
- Patient should be able to understand the delivery system of the medication and the importance of reporting any complication to the prescribing physician in a timely manner.

Expected Patient Course

- Patient is considered to be a good candidate for the therapy.
- Switch to oral IR carbidopa/levodopa.
- Evaluation by PT/OT +/- Neuropsychology.
- Scheduling with the GI Service for PEG J placement.
- Training about stoma care.
- After PEG J is inserted, patient will go home and will return for titration 2 weeks after. In the meantime, they will resume usual oral therapy until then.

After Peg J is placed

- Titration occurs as per protocol, preferably on a Monday.
- Communication will occur with patient every afternoon the rest of the week to monitor the therapy and need for further titration.
- If further dose changes are needed, patient can come at 3:30 PM to make changes in the delivery system.
- Once the final dose is achieved, follow up every 2-3 months.

Initiating DUOPA Therapy

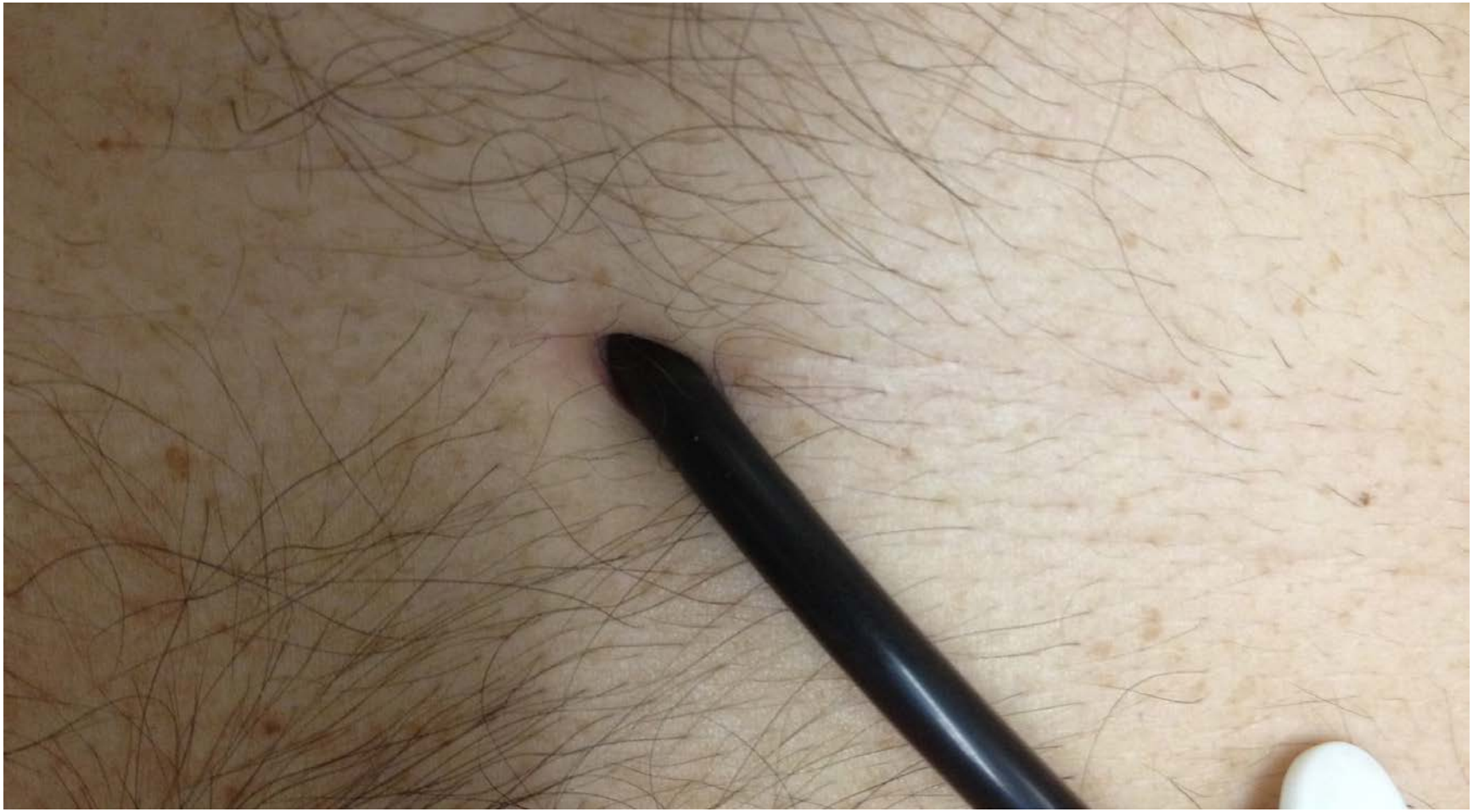
Titrate dose of DUOPA

- Prior to initiating DUOPA, patients should be converted from all other forms of levodopa to oral immediate release carbidopa-levodopa tablets.
- Patients should remain on a stable dose of their concomitant PD medications before initiation of DUOPA infusion.
- Starting dose is divided into Morning Dose and Continuous Dose over 16 hours/day.
- Extra Doses may be given to achieve adequate symptom control.

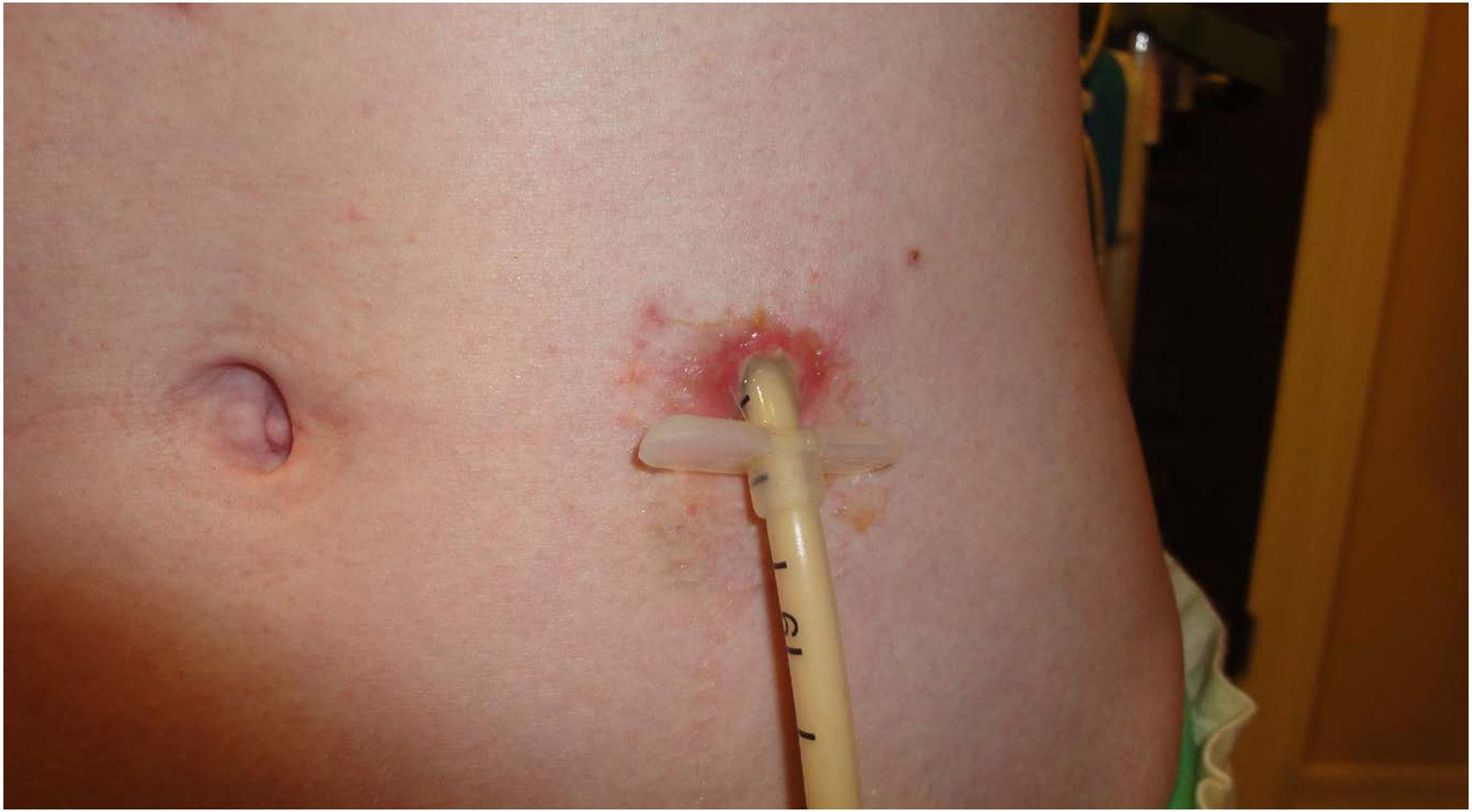
- The daily dose of DUOPA can be titrated as needed, based on the patient's individual clinical response and tolerability after Day 1 of DUOPA treatment and until a stable daily dose is maintained.
- Adjustments to concomitant Parkinson's disease medications may be needed.

DUOPA Prescribing Information, available at www.rxabbvie.com.

“Ideal” Stoma



Not an “ideal” stoma



DUOPA: Contraindications

- DUOPA is contraindicated in patients who are currently taking a nonselective monoamine oxidase (MAO) inhibitor (e.g., phenelzine and tranylcypromine) or have recently (within 2 weeks) taken a nonselective MAO inhibitor.
- Hypertension can occur if these drugs are used concurrently.

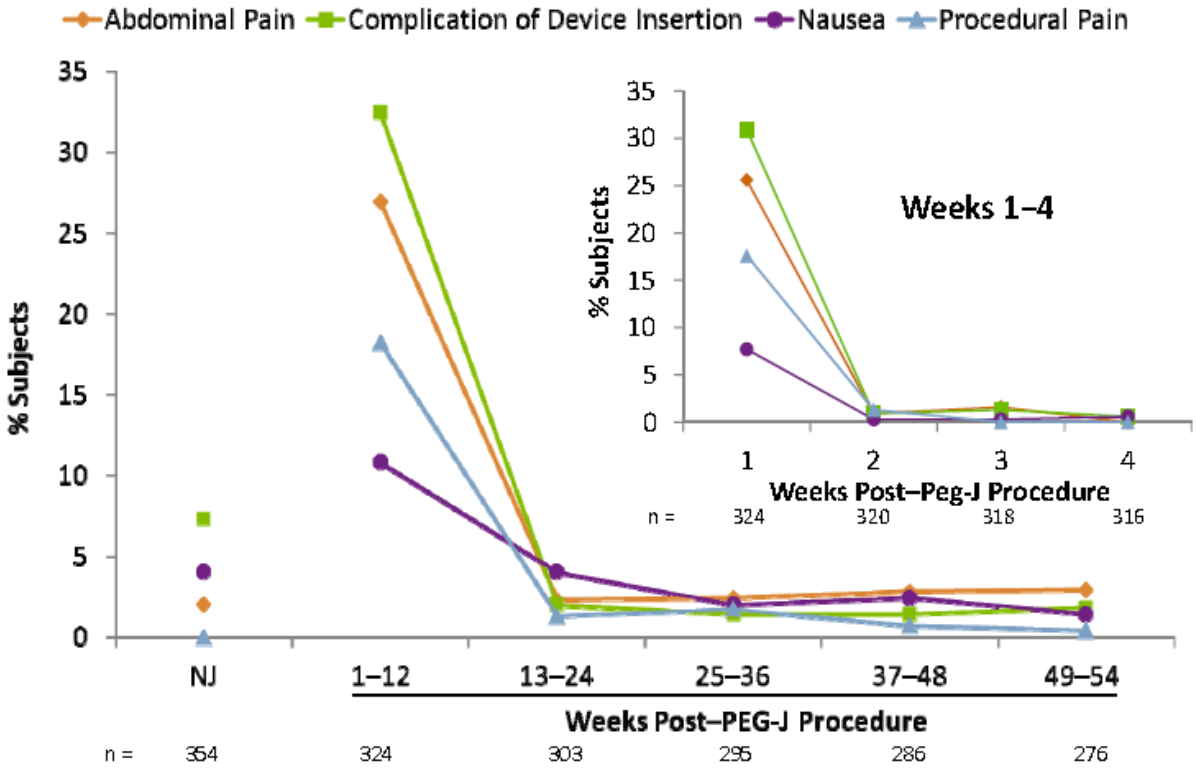
DUOPA Prescribing Information, available at www.rxabbvie.com.

DUOPA: Most Common Adverse Reactions for DUOPA (At Least 7% Greater than Oral Immediate-Release Carbidopa-Levodopa)

- Complication of device insertion
- Nausea
- Depression
- Peripheral edema
- Hypertension
- Upper respiratory tract infection
- Oropharyngeal pain
- Incision site erythema
- Atelectasis

DUOPA Prescribing Information, available at www.rxabbvie.com.

Treatment emergent adverse events



Device associated adverse events

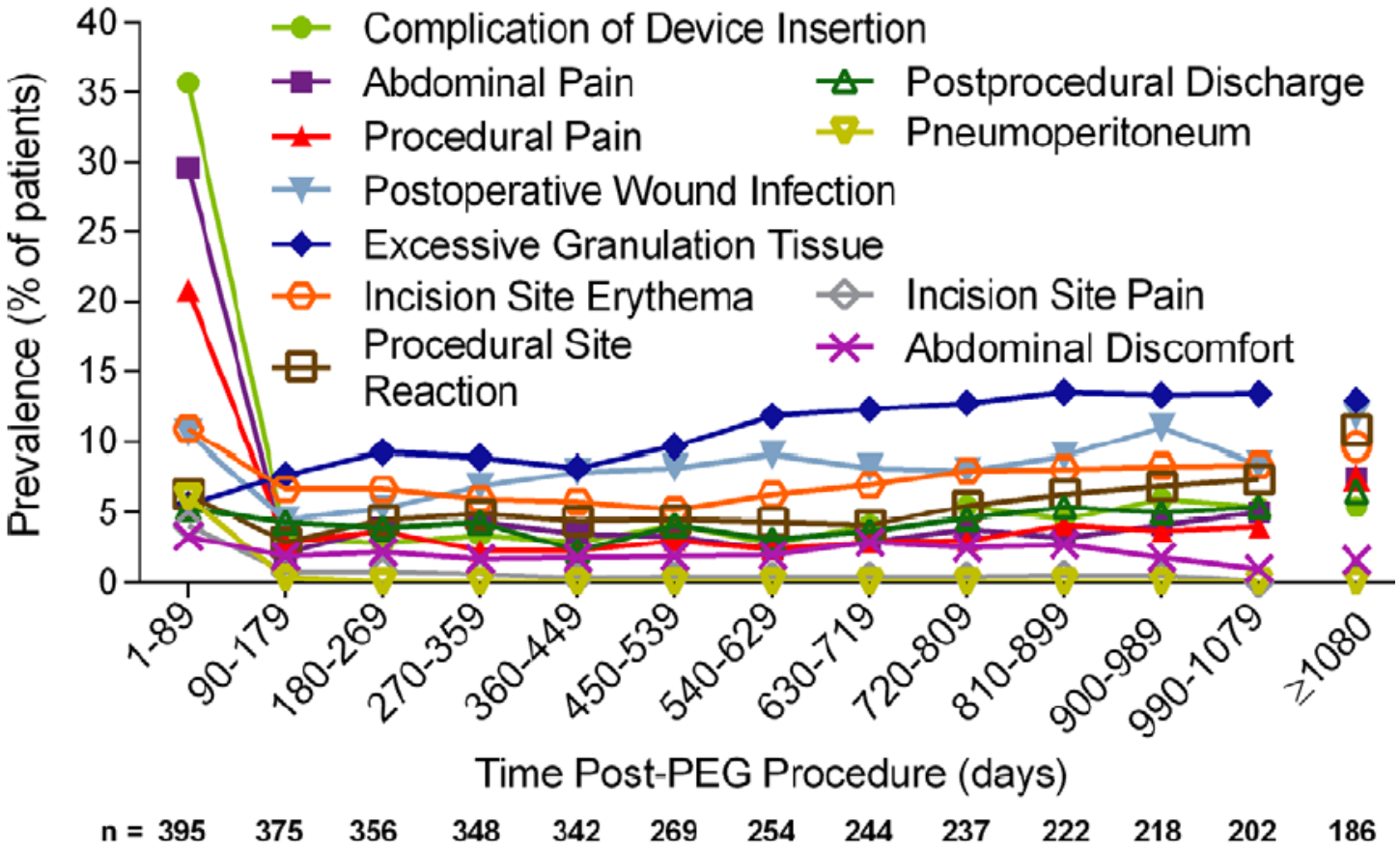


Figure 3. Prevalence of Procedure or Device-Associated Adverse Events Over Time in ≥5% of Subjects (N=395) Receiving Levodopa/Carbidopa Intestinal Gel[4,17]

Abbreviation: PEG, percutaneous endoscopic gastrostomy.

DUOPA: Warnings and Precautions

- Gastrointestinal procedure-related complications may result in serious outcomes, such as need for surgery or death.
- May cause falling asleep during activities of daily living, including the operation of motor vehicles, which may result in accidents.
- Monitor patients for orthostatic hypotension, especially after starting DUOPA or increasing the dose.
- Hallucinations/Psychosis/Confusion: May respond to dose reduction in levodopa.
- Impulse Control Disorders: Consider dose reductions or stopping DUOPA.
- Monitor patients for depression and suicidality.
- Avoid sudden discontinuation or rapid dose reduction to reduce the risk of withdrawal-emergent hyperpyrexia and confusion.
- May cause or exacerbate dyskinesia: Consider dose reduction.
- Monitor patients for signs and symptoms of peripheral neuropathy.

DUOPA Prescribing Information, available at www.rxabbvie.com.

Adverse events

abdominal pain, abdominal discomfort, abdominal distension, flatulence, and pneumoperitoneum.

Table 6. Percentage of Adverse Events of Special Interest Reported in Subjects (n=324) Receiving Levodopa/Carbidopa Intestinal Gel Post Percutaneous Endoscopic Gastrojejunostomy Placement[3,a]

References

1. Duopa [package insert]. North Chicago, IL: AbbVie.
2. Slevin JT, Fernandez HH, Zadikoff C, et al. Long-term safety and maintenance of efficacy of levodopa-carbidopa intestinal gel: an open-label extension of the double-blind pivotal study in advanced Parkinson's disease patients. *J Parkinsons Dis*. 2015;5(1):165-174.
3. Fernandez HH, Standaert DG, Hauser RA, et al. Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: final 12-month open-label results. *Mov Disord*. 2015;30(4):500-509.
4. Lang AE, Rodriguez RL, Boyd JT, et al. Integrated safety of levodopa-carbidopa intestinal gel from prospective clinical trials [published online ahead of print Decemeber 23, 2015]. *Mov Disord*. doi: 10.1002/mds.26485.
5. Nyholm D, Klangemo K, Johansson A. Levodopa/carbidopa intestinal gel infusion long-term therapy in advanced Parkinson's disease. *Eur J Neurol*. 2012;19(8):1079-1085.
6. Cáceres-Redondo MT, Carrillo F, Lama MJ, et al. Long-term levodopa/carbidopa intestinal gel in advanced Parkinson's disease. *J Neurol*. 2014;261(3):561-569.
7. Sensi M, Preda F, Trevisani L, et al. Emerging issues on selection criteria of levodopa carbidopa infusion therapy: considerations on outcome of 28 consecutive patients. *J Neural Transm*. 2014;121(6):633-642.
8. Zibetti M, Merola A, Ricchi V, et al. Long-term duodenal levodopa infusion in Parkinson's disease: a 3-year motor and cognitive follow-up study. *J Neurol*. 2013;260(1):105-114.
9. Antonini A, Ray Chaudhuri K, Yegin A, Bergmann L, Poewe W. Global long-term registry on efficacy and safety of Duodopa in patients with advanced Parkinson's disease in routine care (GLORIA) – interim results on non-motor symptoms. Presented at: 10th International Congress on Non-Motor Dysfunctions in Parkinson's Disease and Related Disorders; December 4-7, 2014; Nice France.