ACØRDA THERAPEUTICS

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Safety and Efficacy of Inbrija (levodopa inhalation powder, CVT-301) on Motor Function During OFF Periods in Patients With Parkinson's Disease

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As Parkinson's disease advances, patients will experience OFF periods, which is when Parkinson's disease symptoms return despite baseline oral therapies. Inbrija® (CVT-301), an inhaled levodopa, is indicated for treatment of OFF episodes in patients with PD on a carbidopa/levodopa regimen. This poster reviews Inbrija's efficacy and safety and will provide insight into clinical experience and use.

Parkinson's Disease and OFF Periods

- Most patients with Parkinson's disease (PD) will experience episodic re-emergence of Parkinsonian symptoms with disease progression, called OFF periods[1,2]
  - OFF periods may include motor and non-motor symptoms
  - ON periods, in contrast, are times when symptoms are well controlled
- Baseline dopaminergic therapy aims to reduce OFF periods, but OFF periods can reappear despite therapy[3,4]
- Most patients with PD either already have, or will experience, OFF periods[5,6]
- OFF periods can be unexpected and unpredictable, and can occur at any time during the day[2,7,8]
- OFF periods have a major negative impact on healthcare costs and patient quality of life[9-11]

Treatment Options

- Oral levodopa (LD) is the most effective treatment for PD motor symptoms,[12] however, there are limitations to oral LD administration:
  - LD plasma half-life is short, peak plasma levels are not obtained until about 1 hour after oral dosing,[13] and gastrointestinal dysfunction and food effects impact LD absorption, leading to unpredictable control of OFF periods[14,15]
- Until 2019, the only treatment for the rapid relief of OFF periods was subcutaneous apomorphine. It is a subcutaneously injected medication that can cause severe nausea and vomiting, and requires premedication with an antiemetic[16]

Inbrija® (CVT-301, levodopa inhalation powder)

- Inbrija is an LD oral inhalation powder approved for treatment of OFF episodes in patients who are already on an oral dopa decarboxylase inhibitor/LD (DDI/LD) (eg, Sinemet) regimen[17,18]

- Breath-actuated inhaler, about 5 inches long
- LD is formulated as a large-particle dry inhalation powder, supplied in capsules
- 1 dose consists of 2 capsules (84 mg)
- Provides consistent and precise pulmonary delivery of LD to the systemic circulation[19,20]
- To be taken when patient has an OFF period in between doses of regular CD/LD
- No more than 5 doses (10 capsules) in a day

Table 1. Key Inbrija Clinical Trials

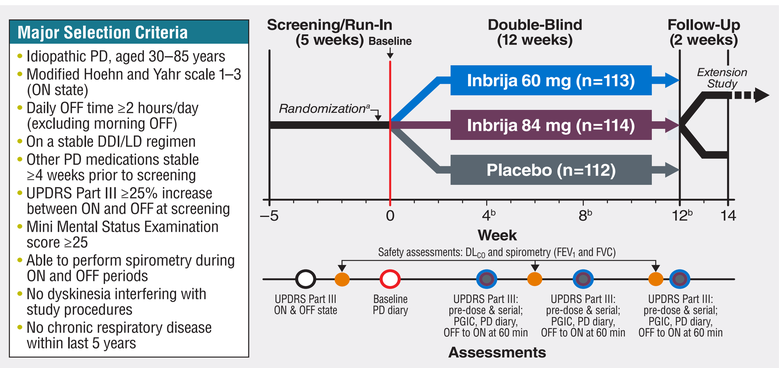
Study	Study Type	Purpose	Number of Randomized Subjects	Treatment[a]	Treatment Duration	Reference
Multiple-Dose Studies in PD Subjects						
SPAN-PD CVT-301-004 *Pivotal phase 3 study*	Multicenter, randomized, double-blind, placebo-controlled	Efficacy and safety study	339	• Inbrija 60 mg • Inbrija 84 mg • Placebo	12 weeks	LeWitt PA, et al. *Lancet Neurol.* 2019; 18(2):145-154.
CVT-301-004E	Multicenter, dose-level blinded, long-term extension study[b]	Pulmonary safety, safety	325	• Inbrija 60 mg • Inbrija 84 mg	12 months	Farbman ES, et al. *Neurology.* 2019;92 (15 Supplement): P2.8-048. [abstract]
CVT-301-005	Multicenter, randomized, open-label, with observational cohort control	Long-term pulmonary safety study	408	• Inbrija 84 mg	12 months	Grosset DG, et al. *Parkinsonism Relat Disord.* 2020;71:4-10.
Single-Dose Studies in PD Subjects						
CVT-301-009	Multicenter, randomized, double-blind, placebo-controlled	Safety and tolerability study of Inbrija when administered with the first oral dose of CD/LD of the day to treat early morning OFF symptoms	36	• Inbrija 84 mg • Placebo	2-way crossover: 2 dosing days separated by 1- to 7-day interval	Hauser RA, et al. *Parkinsonism Relat Disord.* 2019;64:175-180.
CVT-301-012	Multicenter, randomized, open-label	Pharmacokinetic evaluation of a single inhaled dose of Inbrija administered with oral CD and a single orally administered dose of CD/LD, under fed conditions	23	• Inbrija 84 mg+ oral 25 mg CD • Oral CD/LD (Sinemet 25 mg/100 mg)	2-way crossover: 2 dosing days separated by 48-hour interval	Safirstein B, et al. *Clin Ther.* In press.

[a]All patients were on a standard oral DDI/LD regimen. [b]Extension of SPAN-PD study, but also enrolled former patients from CVT-301-005, CVT-301-009, and from an earlier study (CVT-301-003), if eligible.
CD, carbidopa; DDI, dopa decarboxylase inhibitor; LD, levodopa; PD, Parkinson's disease.

SPAN-PD Efficacy and Safety Study[18]

- Pivotal phase 3 double-blind, placebo-controlled study

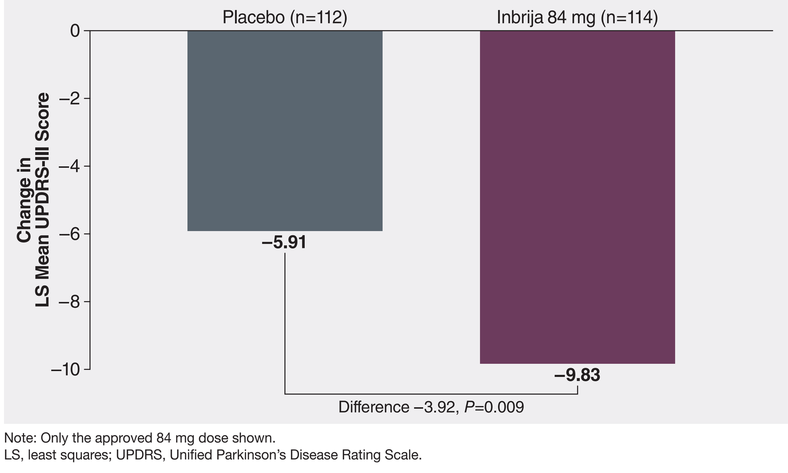
Figure 1. SPAN-PD Study Design



[a]Randomization was stratified by modified H&Y in ON state (<2.5 vs ≥2.5), and FEV$_1$ and FEV$_1$/FVC (FEV$_1$ <60% or FEV$_1$/FVC <70% vs FEV$_1$ ≥60% and FEV$_1$/FVC ≥70%). [b]Subjects had received their morning DDI/levodopa dose prior to coming to the clinic and were in an ON state. DDI, dopa decarboxylase inhibitor (either carbidopa or benserazide); DL$_{CO}$, carbon monoxide diffusing capacity; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; H&Y, Hoehn and Yahr scale; LD, levodopa; PD, Parkinson's disease; PGIC, Patient Global Impression of Change scale; UPDRS, Unified Parkinson's Disease Rating Scale.

- The *primary endpoint* was change in Unified Parkinson's Disease Rating Scale (UPDRS) Part III (motor) score from pre-dose to 30 minutes post-dose with Inbrija 84 mg vs placebo at week 12, when subjects were evaluated in-office during an OFF period
- The UPDRS is a rating tool used to gauge the course of PD in patients and consists of 5 parts, of which the motor assessment is Part III. A lower UPDRS Part III score is better

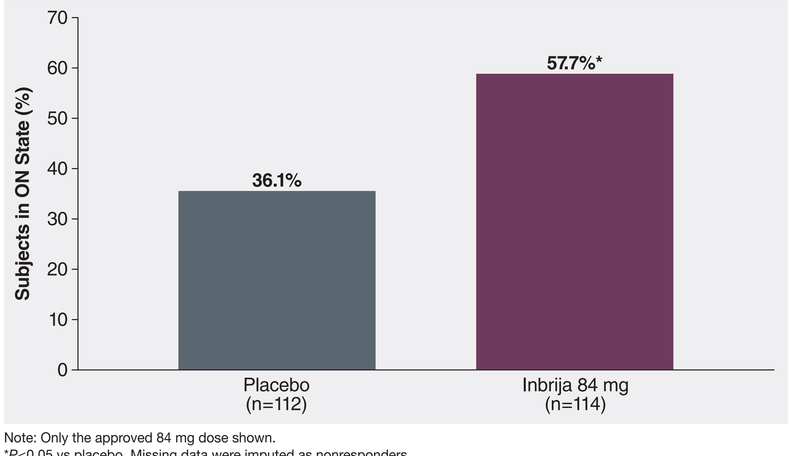
Figure 2. Primary Endpoint: UPDRS Part III Score Change at Week 12 for Inbrija 84 mg vs Placebo



Note: Only the approved 84 mg dose shown.
LS, least squares; UPDRS, Unified Parkinson's Disease Rating Scale.

- The improvement in UPDRS Part III score from pre-dose to 30 minutes postdose was significantly greater in the Inbrija 84-mg dose group vs placebo during the in-office evaluation at week 12
- A key secondary endpoint was the proportion of subjects achieving an ON state within 60 minutes of treatment and remaining ON at 60 minutes at week 12

Figure 3. Proportion of Subjects in ON State at 60 Minutes Postdose at Week 12



Note: Only the approved 84 mg dose shown.
*P<0.05 vs placebo. Missing data were imputed as nonresponders.

- At week 12, a higher proportion of subjects in the Inbrija vs placebo groups achieved an ON state within 60 minutes of treatment and remained ON at 60 minutes

Safety

Table 2. Treatment-Emergent AEs ≥4% in Any Dose Group

Preferred Term, n (%)	Placebo (n=112)	Inbrija 60 mg (n=113)	Inbrija 84 mg (n=114)
Any treatment-emergent AEs	49 (44)	64 (57)	66 (58)
Cough	2 (2)	17 (15)	17 (15)
URI	3 (3)	2 (2)	7 (6)
Nausea	3 (3)	0	6 (5)
Sputum discolored	0	0	6 (5)
Dyskinesia	0	5 (4)	4 (4)
Fall	2 (2)	5 (4)	3 (3)
Throat irritation	0	8 (7)	1 (1)
Dizziness	5 (4)	2 (2)	1 (1)

AEs, adverse events; URI, upper respiratory tract infection.

- Cough was the most common adverse event (AE) in the Inbrija groups vs placebo (15% vs 2%, reported once/subject). Most AEs of cough in the Inbrija groups started within the first 30 days of treatment, and were generally assessed as mild or moderate in intensity
- 1 patient receiving Inbrija 60 mg reported a severe cough. Three patients (1 receiving 60 mg; 2 receiving 84 mg) had an AE of cough that led to study withdrawal
  - The prevalence of cough was not dose-dependent; ~15% of patients in each Inbrija group had drug-related cough
- Other commonly reported AEs in the Inbrija 84 mg vs placebo group included upper respiratory tract infection (6% vs 3%), nausea (5% vs 3%), and sputum discoloration (5% vs 0%, respectively)
- Treatment-emergent AEs led to study withdrawal of 9 subjects in the Inbrija group and 3 in the placebo group. Cough led to the withdrawal of 3 subjects (84 mg=2 and 60 mg=1) in the Inbrija groups
- 11 subjects reported at least 1 serious AE (84 mg=2, 60 mg=6, and placebo=3). 2 subjects in the 60 mg group reported chest pain
- A completed suicide occurred in the 60 mg group, which was considered not related to the study drug by the investigator

CVT-301-009 Safety and Tolerability Study of Inbrija to Treat Early Morning OFF Symptoms[21]

- The purpose of this study was to evaluate the acute safety and tolerability of Inbrija given with the first oral CD/LD dose of the day, during early morning OFF
- The results of this study demonstrated that Inbrija 84 mg taken during an early morning OFF period together with routine oral CD/LD therapy was well-tolerated in subjects with PD

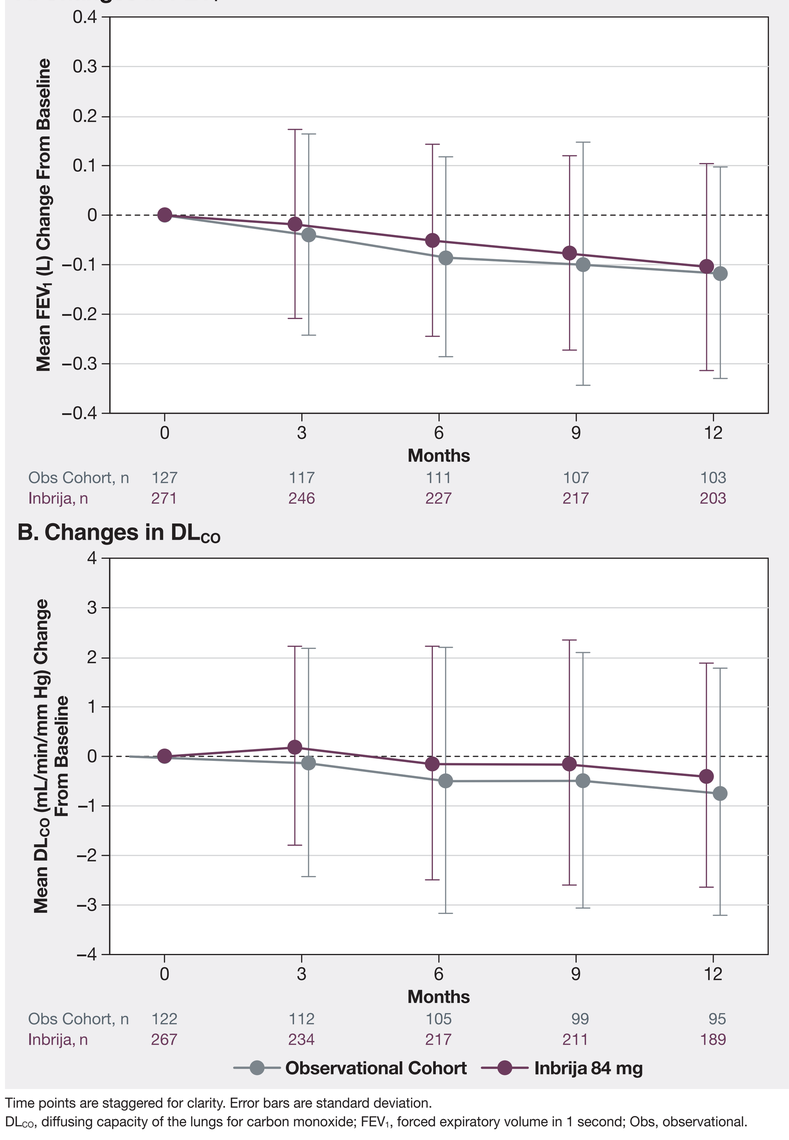
CVT-004E Pulmonary Safety Study[22]

- Dose-level blinded, long-term extension study of SPAN-PD
- Subjects were randomized to Inbrija 60 mg or 84 mg
- The *primary objective* was to determine pulmonary safety over the 12-month treatment period using a number of lung function measures by spirometry
  - *Forced expiratory volume in 1 second* (FEV$_1$), *forced vital capacity* (FVC), and the FEV$_1$/FVC ratio allow for determination of obstructive or restrictive lung disease
  - *Carbon monoxide diffusion capacity* (DL$_{CO}$) is a measure of gas exchange across the alveolar capillary membrane
- Pulmonary safety is important as Inbrija is an inhaled dry powder that enters the lungs for pulmonary delivery of LD
- There were no consistent, notable changes in chronic pulmonary safety as measured by spirometry and DL$_{CO}$, demonstrating the pulmonary safety of up to 15 months of Inbrija treatment

CVT-301-005 Long-Term Pulmonary Safety Study[23]

- CVT-301-005 was a randomized, open-label study with an observational cohort to study pulmonary safety of Inbrija 84 mg over 12 months
- As in 004E, this study assessed pulmonary safety, but with a different set of subjects and with the ability to compare with an observational cohort of subjects with PD who were not taking Inbrija

Figure 4. Changes in Lung Function Over 12 Months



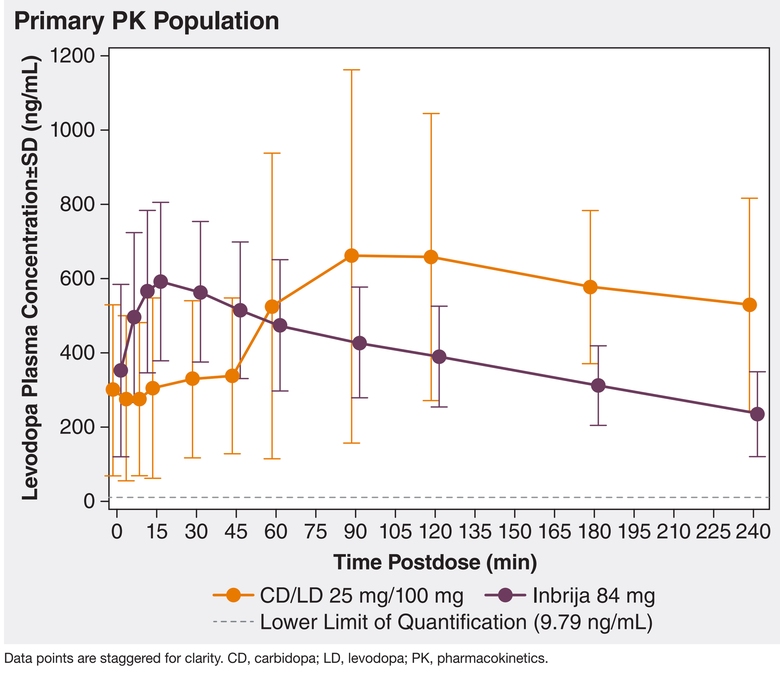
Time points are staggered for clarity. Error bars are standard deviation.
DL$_{CO}$, diffusing capacity of the lungs for carbon monoxide; FEV$_1$, forced expiratory volume in 1 second; Obs, observational.

- Declines in pulmonary function observed over 12 months were similar to those observed in CVT-301-004E and there were no notable differences between the Inbrija and the observational cohorts as measured by FEV$_1$, FVC, FEV$_1$/FVC, and DL$_{CO}$
- Inbrija has no particular pulmonary safety risks associated with the dry powder inhalation system for patients in this PD population

CVT-301-012 Pharmacokinetic Study of Inbrija in Fed Subjects with PD[20]

- The *primary objective* was to investigate the pharmacokinetics of Inbrija administered with CD compared with orally administered CD/LD (Sinemet) in subjects with PD under fed conditions
- Each dosing period was 1 day, and subjects took a single dose of Inbrija 84 mg (+25 mg CD) or a regular oral CD/LD (25 mg/100 mg Sinemet) dose and LD blood concentrations were measured over the next 4 hours
- Study drugs were taken 4 to 5 hours after the subjects' previous routine morning oral CD/LD dose
- Subjects ate a standardized high-fat, high-protein meal just before taking the test drug

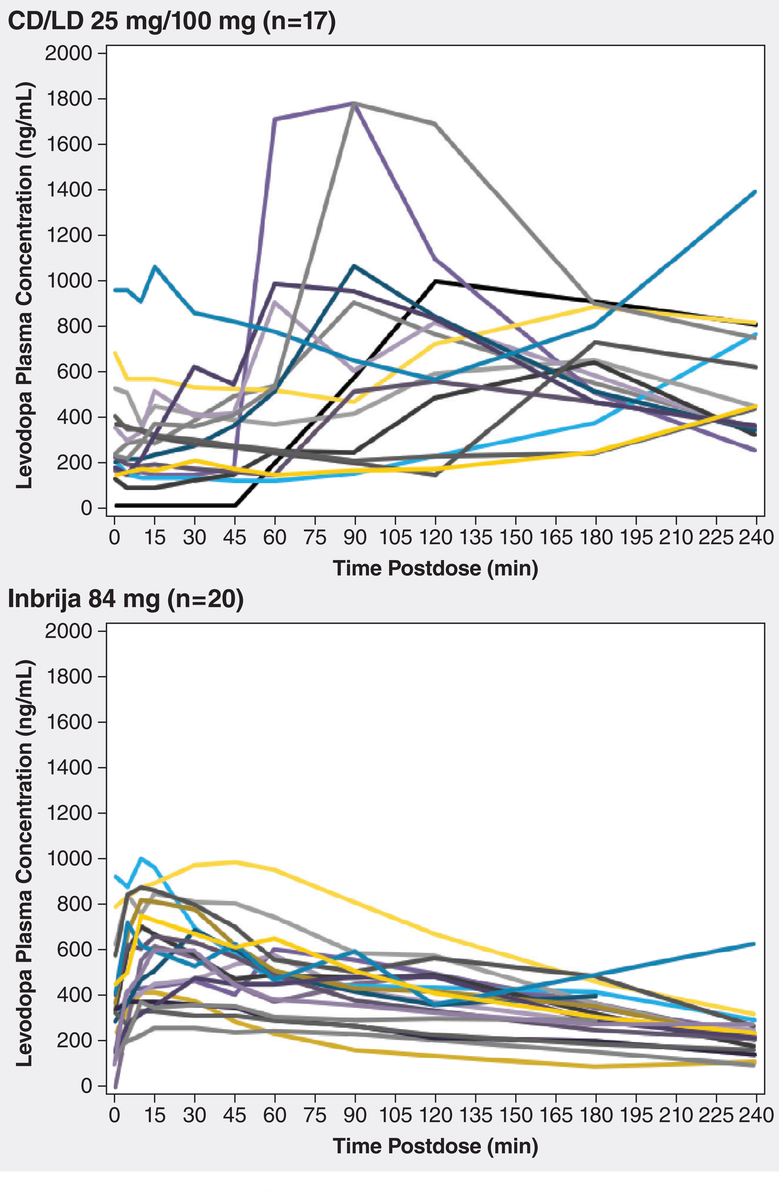
Figure 5. Mean Plasma Levodopa Profiles After a Single Dose of CD/LD (25 mg/100 mg) or Inbrija 84 mg



Data points are staggered for clarity. CD, carbidopa; LD, levodopa; PK, pharmacokinetics.

- After a single inhaled dose of Inbrija 84 mg, plasma LD levels rose rapidly, with a mean increase of ~140 ng/mL by 5 minutes and a mean increase of ~240 ng/mL by 15 minutes
- In contrast, after a single oral dose of CD/LD 25 mg/100 mg, an increase in LD plasma concentrations was not seen until 1 hour postdose

Figure 6. Individual Plasma Levodopa Profiles After a Single Dose of CD/LD (25 mg/100 mg) or Inbrija 84 mg



- The between-subject LD plasma variability for Inbrija 84 mg was generally less than that for oral CD/LD 25mg/100 mg
- Study demonstrates that by bypassing the gastrointestinal tract, Inbrija can raise LD blood concentrations more rapidly than oral LD

Overall Conclusions From Clinical Program

- Inhaled Inbrija 84 mg showed significant improvement in UPDRS Part III (motor) score, as measured 30 minutes postdose at week 12. Improvement was seen as early as 10 minutes postdose
- More subjects in Inbrija groups than in placebo groups turned ON within 60 minutes of treatment and continued to remain ON at 60 minutes
- Inbrija can be used to treat early morning OFF periods
- Inbrija 84 mg used for up to 12 months produced no clinically significant differences in pulmonary function compared with an OC not treated with Inbrija
- Inbrija 84 mg increased plasma LD concentration as soon as 5 minutes after administration and reached its maximum concentration in a median time of 15 minutes versus oral CD/LD, which showed no increase until 60 minutes and reached its maximum concentration in a median of 120 minutes
- LD plasma concentration variability among subjects was lower after Inbrija administration than after oral CD/LD dosing
- Inbrija safety profile was generally consistent across studies
- The most common AE associated with Inbrija is cough, found in ~15% of subjects in the SPAN-PD trial
- Reported AEs with Inbrija were generally consistent with known AEs recognized with CD/LD use, with the addition of the pulmonary-related AEs (eg, cough)

Inbrija in the Clinic

- Inbrija is an orally inhaled dry powder formulation of LD that allows LD to enter the lungs first, then the blood and brain. Inbrija does not depend on the digestive tract for absorption
- Inbrija can help manage OFF periods
- Inbrija may start to work in as soon as 10 minutes
- Inbrija is for use as needed, to be taken as prescribed when symptoms of OFF periods start to return (1 dose per OFF period, no more than 5 doses a day)
- Inbrija does not replace regular CD/LD therapy but is used as an additional on-demand therapy

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Disclosures Cathi A. Thomas has served on Acorda Therapeutics advisory boards. Holly Roberts is an employee of, and owns stock in, Acorda Therapeutics.

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