CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203952Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	203952	**Reviewer:** Kelly M. Kitchens, Ph.D.	
Submission Date:	July 11, 2014		
Division:	Division of Neurology Products	**Acting Team Leader:** Okpo Eradiri, Ph.D.	
Applicant:	AbbVie Inc.	**Acting Supervisor:** Paul Seo, Ph.D.	
Trade Name:	Duopa	**Date Assigned:**	July 22, 2014
Established Name:	Carbidopa and Levodopa enteral suspension	**Date of Review:**	December 1, 2014
Indication:	Long-term treatment of motor fluctuations in patients with advanced (b) (4) Parkinson's disease (b) (4)	**Type of Submission:** 505 (b)(2) NDA Resubmission-Class 2	
Formulation/ strengths	Enteral suspension/ 5 mg/mL carbidopa monohydrate and 20 mg/mL levodopa		
Route of Administration	PEG-J		
Type of Review:	Dissolution acceptance criteria		

SUMMARY:

Background:

The current NDA was originally submitted per section 505 (b)(2) on November 16, 2012. The Applicant relies on their own studies conducted to support approval, as well as the FDA's previous findings of safety and effectiveness for Sinemet® (carbidopa and levodopa) Oral Tablets manufactured by Merck and Co. (approved May 2, 1975, under NDA 17555). However, on January 15, 2013, a refuse-to-file (RTF) letter was issued for this NDA due to various CMC, statistical, and clinical issues. Therefore, the NDA was resubmitted on May 28, 2013 to address all of the deficiencies identified in the RTF letter.

The May 28, 2013 submission included a proposed dissolution method and dissolution acceptance criteria for the drug product. The following proposed dissolution method for the testing of the drug product was determined to be acceptable:

USP Apparatus	Rotation Speed	Medium	Volume	Temperature
2 (Paddle)	25 rpm	0.05 M acetate buffer, pH 4.5	500 mL	37°C

However, the dissolution data required for the setting of the dissolution acceptance criteria were very limited, and critical dissolution data throughout the 15 week stability period under refrigeration conditions at 5ºC were lacking. Therefore, due to lack of critical dissolution data needed for the setting of the dissolution acceptance criteria, a Complete Response (CR) action was recommended for NDA 203952 from the Biopharmaceutics perspective. The FDA issued a CR letter for this NDA on March 28, 2014, due to deficiencies related to product quality, CDRH, human factors, and safety issues.

Resubmission:
This Resubmission of NDA 203952, includes the Applicant's responses to the following Biopharmaceutics deficiencies included in the FDA's CR letter dated March 28, 2014:

1. Submit the complete dissolution profile data (*individual, mean, SD, profiles*) for each time point for the dissolution testing of the commercial-scale batches. Provide the dissolution data at the following time points: 15, 20, 30, 40, 50, and 60 minutes (n=12). The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*).

2. We acknowledge your commitment to provide stability data for your drug product under frozen (-20ºC) and refrigeration (5ºC) conditions post-approval. However, for the setting of the specifications of your drug product, you will need to provide data from at least 3 batches at the initial time point and thereafter at 5, 10, and 15 weeks under refrigeration conditions. For this testing, we consider the initial time point when the product is thawed and placed under the 5ºC refrigeration conditions. For the dissolution testing, provide the complete dissolution profile data as described in above Comment 1.

3. In your October 31, 2013 response to our Information Request (IR), you indicated that (b) (4) whereas in your February 7, 2014 IR (b) (4) response, you indicated that a 10-fold difference. Clarify this discrepancy (b) (4)

Review:
The Biopharmaceutics review is focused on the evaluation and acceptability of the information submitted to support the proposed dissolution acceptance criteria.

RECOMMENDATION:

The Applicant provided adequate data to support the proposed dissolution acceptance criterion of Q= (b)(4)% at 40 minutes for carbidopa and levodopa. The following method and acceptance criterion are acceptable for release and stability testing.

USP Apparatus	Rotation Speed	Medium/Temp	Volume	Carbidopa and Levodopa Acceptance Criterion
2 (Paddle)	25 rpm	0.05 M acetate buffer, pH 4.5 at 37°C	500 mL	Q = (b)(4)% at 40 minutes

From the Biopharmaceutics perspective, NDA 203952 for Duopa (carbidopa and levodopa enteral suspension) is recommended for APPROVAL.

Signature

Kelly M. Kitchens -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000336574, cn=Kelly M. Kitchens -S
Date: 2014.12.02 09:21:08 -05'00'

Kelly M. Kitchens, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Signature

Okponanabofa Eradiri, Ph.D.

Digitally signed by Okponanabofa Eradiri, Ph.D.
DN: cn=Okponanabofa Eradiri, Ph.D., o=ONDQA, ou=Biopharmaceutics, email=okpo.eradiri@fda.hhs.gov, c=US
Date: 2014.12.02 10:04:35 -05'00'

Okpo Eradiri, Ph.D.
Acting Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc. ADorantes; PSeo

BIOPHARMACEUTICS ASSESSMENT

Drug Product:

Description: The Sinemet (levodopa-carbidopa) Tablet product is a combination of levodopa and carbidopa for the treatment of the symptoms of idiopathic Parkinson's disease (paralysis agitans). Carbidopa reduces the amount of levodopa required to produce a given response by about 75%, and increases both plasma levels and plasma half-life of levodopa. For the proposed carbidopa and levodopa enteral suspension product, continuous delivery via direct tubing to the intestine avoids the variable gastric emptying time, results in less variability in carbidopa and levodopa plasma concentrations compared to oral dosing and is believed to provide a continuous rather than intermittent stimulation of the dopaminergic receptors in the brain. Carbidopa and levodopa enteral suspension also provides continuous delivery to the upper intestine, where the compounds are rapidly absorbed by an active carrier mechanism localized in the proximal small intestine.

Formulation: Carbidopa and levodopa enteral suspension is a formulation of carbidopa and levodopa delivered from a medication cassette reservoir via the CADD-Legacy® 1400 portable infusion pump into the proximal small intestine through a percutaneous endoscopic gastrostomy with jejunal extension (PEG-J). The drug-device combination product that includes the following elements:

a. The drug product, carbidopa and levodopa enteral suspension, 5 mg/mL or 20 mg/mL in a medication cassette reservoir; and
b. An enteral administration system, known as the Administration System. This includes: a software-driven, ambulatory infusion pump and a percutaneous endoscopic gastrostomy tube (PEG) with jejunal tube (J), plus an optional, temporary nasojejunal (NJ) tube.

The composition of carbidopa and levodopa enteral suspension is described in the following table:

Component	Quality Standard	Function	Amount per mL
Levodopa	USP	Drug Substance	20.0 mg
Carbidopa monohydrate	USP	(b) (4)	5.0 mg
Carmellose sodium [a]	USP		(b) (4)
Purified Water	USP		
			(b) (4)

b. Medication Cassette Reservoir capacity is approximately 100 grams of LCIG.

Dissolution Method:

The following dissolution method was previously determined to be acceptable for carbidopa and levodopa enteral suspension:

USP Apparatus	Rotation Speed	Medium	Volume	Temperature
2 (Paddle)	25 rpm	0.05 M acetate buffer, pH 4.5	500 mL	37°C

FDA's CR Letter Dated March 28, 2014

BIOPHARMACEUTICS DEFICIENCIES and APPLICANT's RESPONSES:

Complete Response Issue #1:
Submit the complete dissolution profile data (*individual, mean, SD, profiles*) for each time point for the dissolution testing of the commercial-scale batches. Provide the dissolution data at the following time points: 15, 20, 30, 40, 50, and 60 minutes (n = 12). Report the dissolution data as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*).

Applicant's Response:
The dissolution method described in Module 3, Section 3.2.P.5.2 (pH 4.5, **USP apparatus** (b) (4) at 25 rpm) was used to obtain the data requested. According to the method, the results are reported as a cumulative percentage based on the label claim (20 mg/mL and 5 mg/mL for levodopa and carbidopa monohydrate, respectively). The complete dissolution profile data from the time points covering 0 weeks, 5 weeks and 8 weeks for the 3 commercial scale batches is contained within Module 3, Section 3.2.P.5.6. As noted above, the remaining time points covering 10 weeks, 12 weeks, and 15 weeks will be submitted within 2 months of the complete response resubmission.

Note: AbbVie will confirm the appropriateness of the previously proposed dissolution limits pending availability of the 15-week stability results from 3 commercial scale batches manufactured (b) (4) and submit this to NDA 203952 during the complete response review.

Summary of submitted documents:
3.2.P.5.6 Justification of Specifications, Dissolution
3.2.P.5.2 Dissolution Test Procedure RTM.C5531

Reviewer's Assessment: SATISFACTORY
On September 11, 2014, the Applicant submitted an amendment to provide the full 15-week stability data (10 weeks, 12 weeks, and 15 weeks), including dissolution profiles from 3 commercial lots.

Reviewer's summary of Justification of Specifications:

Table 1. Batch Information for LCIG Commercial-Scale Batches Evaluated in the Dissolution Assessment

Lot Number	Clinical Trial	Date of Manufacture	Drug Substance Manufacturer	(b) (4)
12D11G07	Not applicable	11 Apr 2012	(b) (4	(b) (4)
12H09G07	M12-920	09 Aug 2012		
12J18G15	M12-920	12 Oct 2012		
13D11G13	S187.3.005	11 Apr 2013		
13D18G21	S187.3.005	18 Apr 2013		
13E10G08	Not applicable	10 May 2013		
13F13G15	S187.3.005	13 Jun 2013		
13F20G23	S187.3.005	20 Jun 2013		
13H20G20	Not applicable	20 Aug 2013		
13J16G15	Not applicable	16 Oct 2013		
14D11G14	Not applicable	11 Apr 2014		
14D11G95	Not applicable	11 Apr 2014		
14D12G15	Not applicable	12 Apr 2014		

Table 2. Detail of Dissolution at 40 Minutes, Commercial-Scale Batches

Lot Number	Levodopa (% Label Claim)			Carbidopa Monohydrate (% Label Claim)			(b) (4)
	Mean	Lowest Individual	Highest Individual	Mean	Lowest Individual	Highest Individual	
12D11G07							
12H09G07							
12J18G15							
13D11G13							
13D18G21							
13E10G08							
13F13G15							
13F20G23							
13H20G20							
13J16G15							
14D11G14 (Initial)							
14D11G14 (10wk)							
14D11G95 (Initial)							
14D11G95 (10wk)							
14D12G15 (Initial)							
14D12G15 (10wk)							

Figure 4. Dissolution of Levodopa: LCIG Commercial-Scale Batches

(b) (4)

Figure 5. Dissolution of Carbidopa Monohydrate: LCIG Commercial-Scale Batches

(b) (4)

- The complete dissolution profiles are included for the ongoing 15-week confirmatory stability study. All results meet the Q=(b) (4)% criterion, with many samples requiring stage 2 evaluation due to the variability of the 40-minute point on the rising portion of the profile. No stability trend is apparent, other than the expected decline in carbidopa monohydrate potency.

Figure 8. Levodopa Dissolution Profiles for LCIG Lot 14D11G14, Stored at 5°C (Mean ± Standard Deviation)

(b) (4)

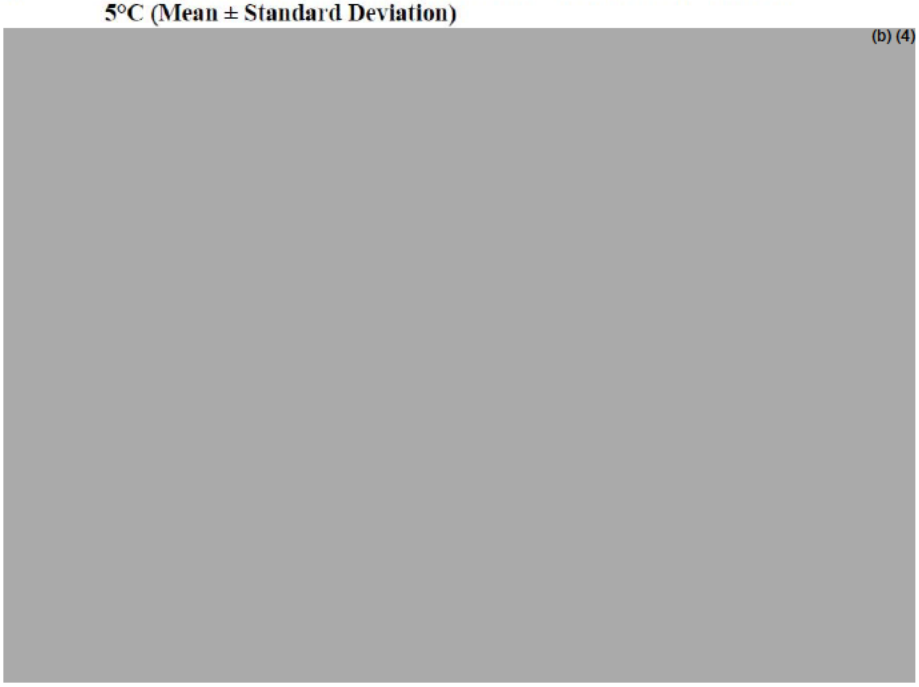

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Table 8. Carbidopa Monohydrate Dissolution Stability Results, Mean of 12, Lot 14D12G15 (continued)

Dissolution (% label claim)						
15 Weeks						
Minutes	**15**	**20**	**30**	**40**	**50**	**60**
1	(b) (4)					
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean						
Std. Dev.						

Reviewer's Comments:

- On August 18, 2014, the following Information Request (IR) was communicated to the Applicant:

  Submit the complete dissolution profile data (individual, mean, SD) for each time point for the dissolution testing of the following commercial-scale batches:
  Lot numbers 12D11G07, 12H09G07, 12J18G15, 13D11G13, 13D18G21, 13E10G08, 13F13G15, 13F20G23, 13H20G20, and 13J16G15.

  On August 22, 2014, the Applicant submitted the following response:

  The dissolution profile data (individual, mean and standard deviation) for the requested commercial-scale lots are provided in Table 1 through Table 10.

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Table 10. Dissolution Data for LCIG Lot Number 13J16G15

Levodopa %LA	Pull-time (minutes) 15	20	30	40	50	60
1	(b) (4)					
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean						
Std. Dev.						

Table 10. Dissolution Data for LCIG Lot Number 13J16G15 (continued)

Carbidopa %LA	Pull-time (minutes) 15	20	30	40	50	60
1	(b) (4)					
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean						
Std. Dev.						

- The approved dissolution method, as described in test procedure RTM.C5331 "Dissolution Test Method and Analytical Finish by HPLC/UV for Levodopa-Carbidopa Intestinal Gel 20 mg per mL - 5 mg per mL," uses the USP apparatus 2 (paddle) (b) (4) However, in the Applicant's response to the CR Issue #1, the Applicant stated that (b) (4) was used to obtain the data requested.

- In addition, it was observed that Levodopa dissolution was [redacted] after 8 weeks than dissolution at 0 and 5 weeks.
- Therefore, the following IR was communicated to the Applicant on October 9, 2014:

    1. In your Complete Response Resubmission dated July 11, 2014, your response to Product Quality Issue 3 states "The dissolution method described in Module 3, Section 3.2.P.5.2 (pH 4.5, USP apparatus [redacted] at 25 rpm) was used to obtain the data requested." The approved dissolution method, as described in test procedure RTM.C5331 "Dissolution Test Method and Analytical Finish by HPLC/UV for Levodopa-Carbidopa Intestinal Gel 20 mg per mL - 5 mg per mL," uses the USP apparatus 2 (paddle) [redacted] Confirm that the following dissolution method was used to obtain the requested data:

USP Apparatus	Rotation Speed	Medium	Volume	Temperature
2 (Paddle)	25 rpm	0.05 M acetate buffer, pH 4.5	500 mL	37°C

    2. Levodopa dissolution is [redacted] after 8 weeks than dissolution at 0 and 5 weeks for lot 14D11G14. Provide an explanation for this observed difference in dissolution.

- On October 14, 2014, the Applicant submitted the following responses:

    IR #1: AbbVie confirms that the information in the table above was utilized to obtain the requested data. The AbbVie response to Product Quality Issue 3 in the Complete Response Resubmission, dated July 11, 2014 contained a typographical error and it should have stated USP Apparatus 2 (Paddle).

    IR #2 (summarized by the Reviewer): [redacted]

- The Applicant's responses are acceptable. The Applicant has satisfactorily addressed the Complete Response Issue #1.

Complete Response Issue #2:

We acknowledge your commitment to provide stability data for your drug product under frozen (-20ºC) and refrigeration (5ºC) conditions post-approval. However, for setting the specifications for your drug product, you will need to provide data from at least 3 batches at the initial time point and thereafter at 5, 10, and 15 weeks under refrigeration conditions. For this testing, we consider the initial time point to be when the product is thawed and placed under the 5ºC refrigeration conditions. For the dissolution testing, provide the complete dissolution profile data as described in the above comment.

Applicant's response:

Data from 3 commercial scale batches for the drug product for the initial, 5 week, and 8 week time points stored at refrigerated conditions are provided within Module 3, Section 3.2.P.8. The remaining time points covering 10 weeks, 12 weeks and 15 weeks will be submitted within 2 months. AbbVie confirms that the initial time point is when product is thawed and placed at refrigerated conditions. The complete dissolution profile data are

contained within Module 3, Section 3.2.P.5.6; however, the single time point dissolution results are contained within Module 3, Section 3.2.P.8 for each lot.

Summary of submitted documents:
3.2.P.5.6 Justification of Specifications, Dissolution
3.2.P.8.1 Stability Summary and Conclusions
3.2.P.8.3 Stability Data for Batch 14D11G14
3.2.P.8.3 Stability Data for Batch 14D11G95
3.2.P.8.3 Stability Data for Batch 14D12G15

Reviewer's Assessment: ***SATISFACTORY***

- The requested data are provided for commercial batches 14D11G14, 14D11G95, and 14D12G15 in detail in the tables and figures submitted in the response to Complete Response Issue #1.
- The Applicant's response is acceptable.

Complete Response Issue #3:
In your October 31, 2013, response to our Information Request (IR), you indicated that (b) (4) whereas in your February 7, 2014, IR response you indicated that (b) (4) a 10-fold difference. Clarify this discrepancy (b) (4)

Applicant's response:
AbbVie acknowledges the discrepancy (a typographical error) between the October 2013 and February 2014 Information Requests. The correct value for the (b) (4) The content of Module 3 is not impacted and no changes to the Module 3 content are being submitted.

Reviewer's Assessment: ***SATISFACTORY***

- The Applicant's response is acceptable. The Applicant previously provided information to satisfactorily explain the decrease in (b) (4) over the course of the shelf-life.

Reviewer's Overall Assessment: ***SATISFACTORY***

- Based on the overall submitted data, carbidopa and levodopa both pass the proposed acceptance criterion of Q= (b) (4)% at 40 minutes at the S2 level.
- The Applicant's proposed dissolution acceptance criteria of Q= (b) (4)% at 40 minutes for carbidopa and levodopa are acceptable.

RECOMMENDATION:

The Applicant provided adequate data to support the proposed dissolution acceptance criteria of Q=(b) (4)% at 40 minutes for carbidopa and levodopa. From the Biopharmaceutics perspective, NDA 203952 for Duopa (carbidopa and levodopa enteral suspension) is recommended for approval.

Clinical Pharmacology Review

NDA#	203952
Date of Original submission:	11/16/12
Date of Resubmission:	5/28/13
Brand Name:	Duopa
Generic Name:	Levodopa-Carbidopa
Administration Route:	Intestinal
Strength and Formulation:	Gel: 20 mg/mL (levodopa) – 5 mg/mL (carbidopa monohydrate)
Sponsor:	AbbVie Inc.
Indication:	long-term treatment of motor fluctuations in patients with advanced (b) (4) Parkinson's disease (PD)
Submission Type:	Standard
CP Reviewer Team:	Bei Yu, Ph.D., Angela Men, M.D., Ph.D., Hongshan Li, Ph.D., Atul Bhattaram, Ph.D.

OCP optional inter-division briefing: Feb 27, 2014.

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

The sponsor resubmitted this 505(b)(2) New Drug Application (NDA) for Levodopa-Carbidopa Intestinal Gel (LCIG). LCIG is a gel formulation of levodopa and carbidopa, delivered from a medication cassette reservoir via the CADD-Legacy® 1400 portable infusion pump into the proximal small intestine through a percutaneous endoscopic gastrostomy with jejunal extension (PEG-J). LCIG has been developed for the long-term treatment of motor fluctuations in patients with advanced (b) (4) Parkinson's disease (PD) (b) (4) With jejunal administration, levodopa can be rapidly absorbed by an active carrier mechanism localized in the proximal small intestine. The delivery of LCIG directly to the jejunum is believed to result in less variability in levodopa and carbidopa plasma concentrations compared to oral dosing and also to provide a continuous rather than intermittent stimulation of the dopaminergic receptors in the brain.

The LCIG formulation is a suspension of 20 mg/mL levodopa and 5 mg/mL carbidopa monohydrate in water. The total daily dose consists of morning dose, the continuous maintenance dose and the doses that can be provided by the extra dose function of the pump (b) (4) ne medication cassette reservoir supplies a daily need of up to 2000 mg levodopa.

The reference listed drug for this 505(b)(2) application is Sinemet® (levodopa-carbidopa) tablets (NDA No. 017555). LCIG was granted Orphan Drug designation by the Office of Orphan Drug Products on January 18, 2000. In November 2011, the Agency agreed that the LCIG System is considered a combination product (drug, pump, and tubing).

The sponsor submitted the original NDA in November 2012, which was refused to file in January 2013 due to filing issues from CMC, Statistics, and Clinical Safety.

This application includes a combined pivotal Phase 3 clinical trial (combination of study S187-3-001 and study S187-3-002 as one pivotal), three long-term Phase 3 supportive studies, and a human pharmacokinetic study.

The LCIG System is currently approved ex-US in 41 countries and marketed in many countries under the trade name Duodopa®.

1.1 RECOMMENDATION

The NDA resubmission is acceptable from a Clinical Pharmacology perspective and the OCP recommends approval for NDA 203952 pending satisfactory agreement with the sponsor on the label.

1.2 PHASE IV COMMITMENT/REQUIREMENT

None.

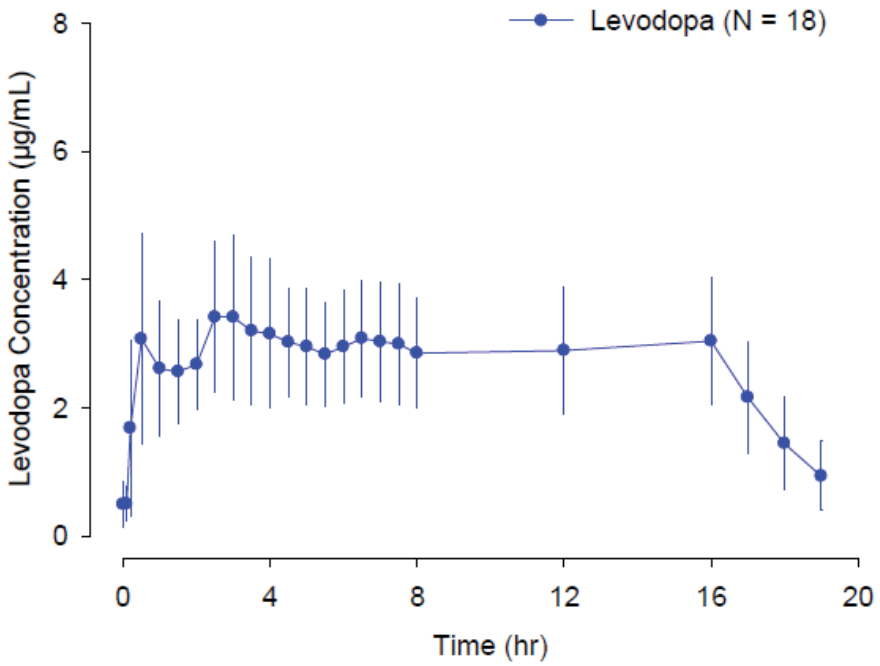
1.3 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY

Following LCIG administration, peak plasma levels of levodopa is reached at median Tmax of 2.5 hours, and maintained consistent levodopa levels over the course of infusion. Following termination of infusion, levodopa levels declined rapidly with average t1/2 of 1.5 hours.

The bioavailability estimate for levodopa from LCIG relative to oral levodopa-carbidopa tablets was 97% (95% confidence interval; 95% to 98%) based on PPK analysis.

The within patient variability of levodopa plasma concentration of LCIG is smaller than that of the oral formulation (8.6% v.s., 15.5%). This indicates lower PK variability of levodopa after LCIG dosing when compared to LC oral formulation. The low PK variability also translated into better clinical response (lower OFF TIME) after LCIG dosing when compared to LC oral formulation (Figure 3).

Plasma concentration (Mean ± SD) versus time profile of levodopa with LCIG 16-hour infusion is shown below:



Signatures
Bei Yu (CP primary reviewer)
Angela Men (CP TL)
Division of Clinical Pharmacology 1

Hongshan Li (PM reviewer)
Atul Bhattaram (PM Secondary Reviewer)

2 QUESTION BASED REVIEW (QBR)

This section only focuses on specific questions.

2.1 Specific Questions

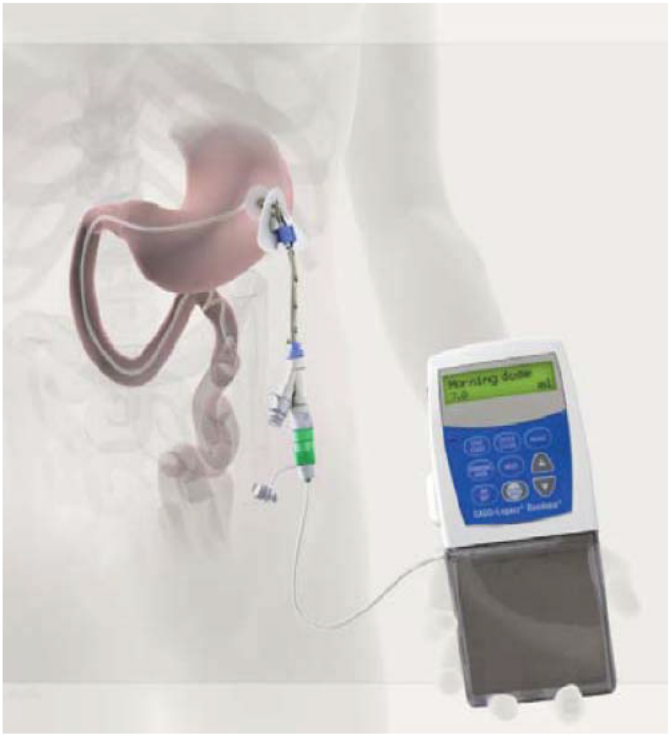
2.1.1 What are the components of the drug product LCIG and LCIG administration system?

LCIG is a suspension of levodopa-carbidopa monohydrate (4:1) in an aqueous carmellose sodium (b) (4) Composition of LCIG, 20 mg/mL-5 mg/mL, commercial formulation which also was used for the PK study and Phase III studies, is showed below:

Component	Composition (% w/w) [a]
Levodopa	(b) (4)
Carbidopa monohydrate	
Carmellose sodium	
Purified Water	

a. (b) (4)

The whole LCIG system includes a medication cassette reservoir with the drug product, an enteral administration system, known as the LCIG Administration System which includes a software-driven, ambulatory infusion pump and a percutaneous endoscopic gastrostomy tube (PEG) with jejunal tube (J), plus an optional, temporary nasojejunal (NJ) tube.



2.1.2 What are the proposed dosages and routes of administration?

LCIG is administered into the jejunum through a percutaneous endoscopic gastrostomy with jejunal tube (PEG-J) using only the CADD®-Legacy 1400 portable infusion pump.
Establishment of the transabdominal port should be performed by a gastroenterologist or other Health Care Provider experienced in this procedure.
The total daily dose consists of morning dose, the continuous maintenance dose and the doses that can be provided by the extra dose function of the pump.

(b) (4)

[redacted]

2.1.3 What are the design features of the clinical pharmacology and clinical studies that were used to support dosing or claims?

The PK profile of levodopa from LCIG was characterized following administration of LCIG (16-hour infusion) in 18 patients with advanced Parkinson's disease. The relative bioavailability of levodopa from LCIG to oral levodopa-carbidopa IR tablets was assessed via a population pharmacokinetics approach. The development program relies on efficacy and safety outcomes from a combined pivotal Phase 3 clinical trial (combination of study S187-3-001 and study S187-3-002 as one pivotal): 12-week, randomized, double-blind, double-dummy, parallel-group, multicenter studies to evaluate the efficacy, safety, and tolerability of LCIG in 71 patients with advanced Parkinson's disease

2.1.4 What are the characteristics of levodopa PK following LCIG administration?

PK of levodopa following LCIG administration was characterized in 18 patients with advanced PD (Study S187-1-002). All patients received their individualized dose of LCIG. The dose/day of LCIG was composed of 3 types of doses: morning dose, continues maintenance dose, and extra doses. The average total LCIG dose on the PK assessment day is: levodopa, 1580 ± 403 mg; carbidopa, 395 ± 101 mg.

Following 16-hour infusion of LCIG, peak plasma levels of levodopa is reached at median Tmax of 2.5 hours, and maintained consistent levodopa levels over the course of infusion. Following termination of infusion at night, levodopa levels declined rapidly with t1/2 of 1.5 hours (please see the figure at Section 1.3).

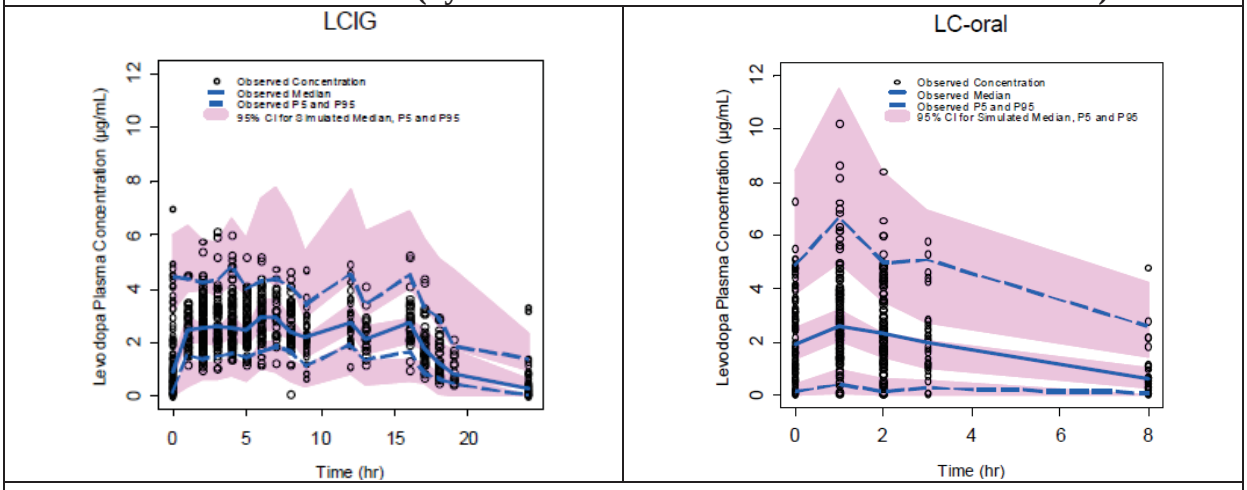
2.1.5 What is the bioavailability of levodopa in LCIG relative to oral formulation (reference product)?

The sponsor assessed the relative bioavailability of levodopa in LCIG compared to oral levodopa-carbidopa IR tablets (LC-oral) via a population pharmacokinetics approach (Studies S187-1-002, S197-3-001, S187-3-002, and S187-3-004).

Based on sponsor's population pharmacokinetics analysis, population mean bioavailability of levodopa in LCIG relative to levodopa in oral formulations was about 97% (with relative standard error = 1%) in patients with advanced Parkinson's diseases. The 95% confidence interval of the relative bioavailability was 95% - 98%.

Figure 1 shows the distribution of levodopa concentrations after LCIG and LC-oral formulation in the Phase III studies. The data were obtained from patients in Phase III studies after they were stabilized on their optimal dose. Figure 1 suggests that a similar range of concentrations is observed in patients receiving LCIG or LC-oral formulation during the initial 1-2h.

Figure 1: Levodopa Plasma Concentrations in Patients After LCIG or LC-oral Formulation Administration (Symbols refer to the observed concentration data)

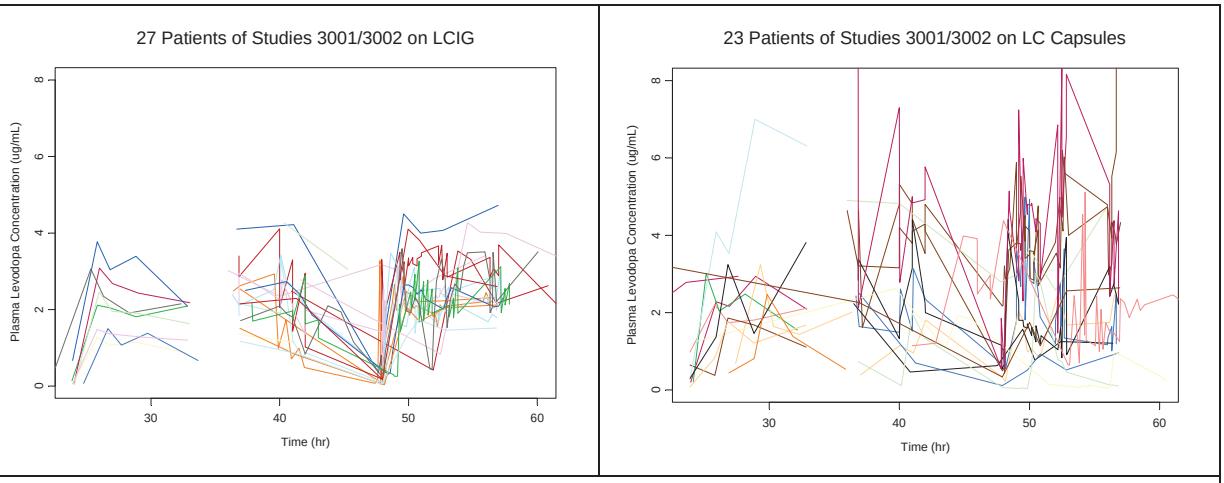


Source: Page 60 of sponsor's population pharmacokinetics report.

2.1.6 How different is intra-subject variability of levodopa plasma concentration (ISVLPC) between LCIG and LC-oral formulation? Do differences in variability of levodopa concentrations translate into better clinical outcomes?

The observed levodopa plasma concentration profiles of individual patients of the two treatments (Figure 2) confirmed that the ISVLPC of LCIG formulation was smaller than the ISVLPC of the oral formulation; the levodopa concentration range of LCIG was significantly smaller than that of the oral capsule when levodopa doses of the two treatments were similar, which implies the comparable patient population in the two arms. The lower variability in plasma concentrations of levodopa after LCIG administration resulted in lower OFF TIME in these patients when compared to oral administration (Figure 3).

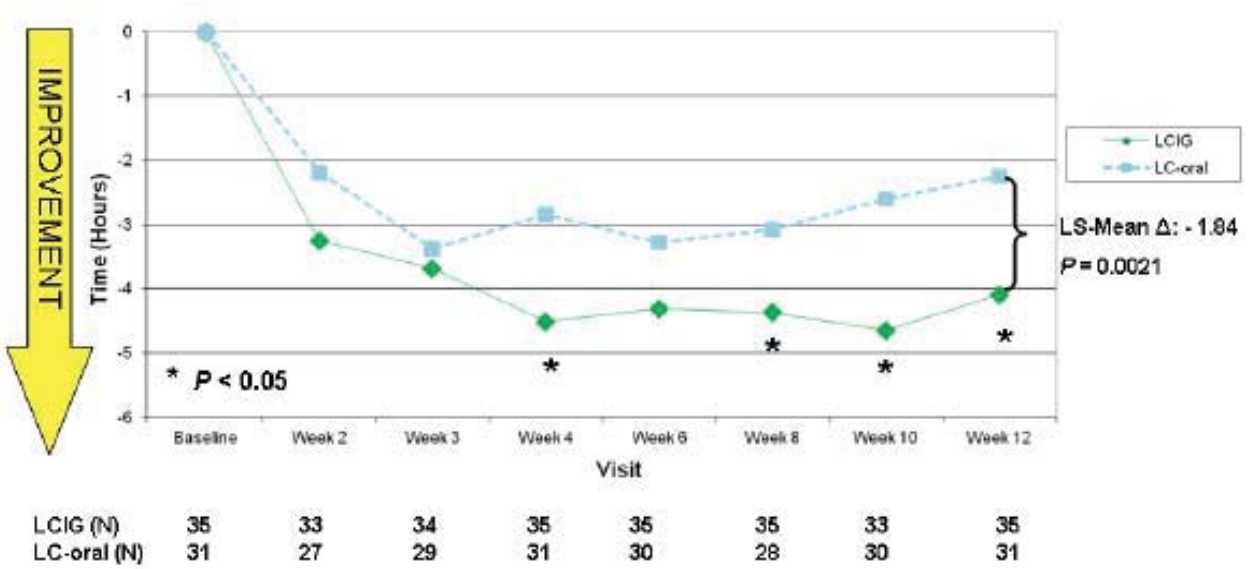
Figure 2: Observed Levodopa Plasma Concentration Profile of Individual Patients by Treatments



Source: Generated by the FDA reviewer based on sponsor's dataset and NONMEM control stream.

Figure 3 shows the longitudinal time course of OFF TIME (Primary endpoint in Phase III clinical studies) after oral or LCIG formulation. Clinical benefit of LCIG was demonstrated over the time course.

Figure 3: Change from Baseline in Average Daily Normalized "Off" Time Based on Parkinson's Disease Diary Data, Mixed Model Repeated Measures.



2.1.7 Is the link between PK of levodopa and efficacy/safety data in the conducted studies adequately characterized?

No, the information collected from the Phase III studies is not sufficient to link PK of levodopa and efficacy/safety data.

Table 1. Phase III Study Information in Patients with Advanced Parkinson's Disease

Study	Number of Patients on LCIG	Number of Patients on LC Capsule	Study Design
3001	15	15	12-week, randomized, double-blind, double-dummy, parallel-group, multicenter studies to evaluate the efficacy, safety, and tolerability of LCIG in 71 patients with advanced Parkinson's disease
3002	12	8	
3004	311	0	12-month open-label, multicenter safety, tolerability, and efficacy of LCIG in 320 patients with advanced Parkinson's disease

Source: Generated by FDA reviewer based on sponsor's study reports on the 3 Phase III studies.

The distribution of the levodopa doses in the Phase III studies are shown in Table 2**.**

Table 2. Sponsor Proposed Levodopa Doses in the Label in Comparison to Levodopa Dose Distribution Data of Phase III Studies 3001, 3002 and 3004

	Morning Dose	Continuous Dose	Extra Dose
			(b) (4)

- Although 311 patients on LCIG completed Study 3004, the PK and efficacy/safety data of those patients cannot be used for a reasonable exposure-response analysis because Study 3004 is an open-labeled study (Table 1).

- Although the sponsor executed two active controlled Phase III studies (Studies 3001 and 3002), total only 30 patients completed Study 3001 with PK data collected, and

15patients were on LCIG and 15 patients were on LC-oral (the active control, over-encapsulated Sinemet). Total only 20 patients completed Study 3002 with PK data collected, and 12 patients were on LCIG and 8 patients were on LC-oral (Table 1). Clinical data collected for those 50 patients of the Phase III controlled studies are not sufficient for a reasonable exposure-response analysis.

In summary, total 27 patients on LCIG and total 23 patients on LC-oral completed the two active controlled Phase III studies (Studies 3001 and 3002) with PK data collected; the PK and efficacy/safety data collected for those 50 patients were not sufficient for a reasonable exposure-response analysis because the sample size was too small to draw a conclusion.

2.1.8 How to interpret the measurable plasma levels of hydrazine in patients following LCIG administration?

Hydrazine is a degradation product of carbidopa in LCIG that is a known toxicant (e.g., its effects of carcinogenicity and genotoxicity) (b) (4)
Plasma concentrations of hydrazine were measured in subgroup of patients (N=17) in Study S187-3-001/S187-3-002, in which 11 patients were with LCIG treatment and 5 were with LC-oral treatment.

One subject with LCIG had detectable levels (in 5 out of 7 samples) of hydrazine, measurable hydrazine concentrations ranged from (b) (4) ng/mL (value of AUC 0-16 was (b) (4) ng.hr/mL). Two of 5 subjects treated with LC-oral showed measurable hydrazine concentrations ((b) (4) and (b) (4) ng/mL) only at 1 time point in the 16-hour sampling interval. The high level of hydrazine due to carbidopa degradation in LCIG is observed.

The half-life of carbidopa in a solution was about 24 hours at room temperature (Pappert et al, 1997; Cedarbaum, 1997). The degradation product, hydrazine from carbidopa Patient S187.3002-111-102 on Study Day 43, as shown in Figure 4, was likely from the morning LCIG dose on Study Day 43. The reason of hydrazine formation is not clear.

Figure 4: Observed Plasma Hydrazine Concentrations in Patient S187.3002-111-102 on Study Day 43

3. DETAILED LABELING RECOMMENDATION

NA

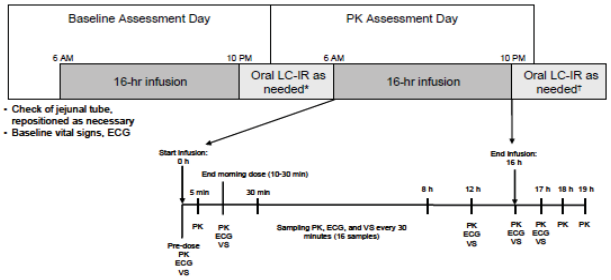
Appendix 1: INDIVIDUAL STUDY REVIEW

PK Study in Patients

Study **S187.1.002**	A Pharmacokinetic Study of Levodopa and Carbidopa Intestinal Gel in Subjects with Advanced Parkinson's Disease.
Investigators	Dag Nyholm, MD, PhD; Prof. Dr. med. Per Lars Anders Odin
Study Site	Quintiles Research Unit, Uppsala, Sweden; Klinikum Bremerhaven Reinkenheide, Bremerhaven, Germany.
Study Period	4/7/10 – 9/30/10
Study Objective	1) to characterize the pharmacokinetics of levodopa, carbidopa and 3-O-methyldopa (3-OMD) metabolite following administration of levodopa-carbidopa intestinal gel (LCIG) in subjects with advanced Parkinson's disease; 2) to evaluate the safety of LCIG in subjects with advanced Parkinson's disease.
Study Design and Dose Administration	The study was a multicenter, multiple-dose, open-label study in 18 subjects with advanced Parkinson's disease. Subjects who were already on a stable dose of LCIG were screened for the study. They remained on their individualized LCIG dose during the study. Subjects who were on approximately 16- or 24-hour LCIG infusion regimen per day were enrolled. Subjects who were on 16-hour infusion per day remained on their normal 16-hour infusion regimen. At baseline, oral levodopa-carbidopa immediate release (IR) was allowed after discontinuation of the pump for up to 3 hours prior to the start of the pump on the PK sampling day (This was ~ equal to 2 half-lives of levodopa in the presence of carbidopa). Subjects who received infusion of more than 16 hours per day prior to the study start had their pumps turned off after 16 hours of infusion on the day prior to the PK sampling day and the PK sampling day. No dosage adjustment (morning dose and continuous flow rate) was done. To compensate for the remaining 8 hours without LCIG infusion, oral levodopa-carbidopa IR was given for up to three hours prior to the start of the pump on the PK day. It was not possible to withhold levodopa-carbidopa treatment in the patient population for a long period of time to completely wash out the residual of oral levodopa-carbidopa treatment before the next LCIG dose. Some residual levodopa-carbidopa from oral administration was expected. This did not significantly affect the characterization of LCIG PK over 16-hour infusion. On the PK day, all subjects received their individualized dose of

LCIG for 16 hours. The administration of any extra doses of LCIG was discouraged during the PK day except when it was deemed absolutely needed. Oral levodopa-carbidopa was not allowed until the last PK sample was collected. After the collection of the last PK sample, the subjects resumed their original levdodopa-carbidopa regimens. A maximum of 24 blood samples (144 mL) were collected from each subject for 19 hours.

Figure 1. Design of Study S187-1-002



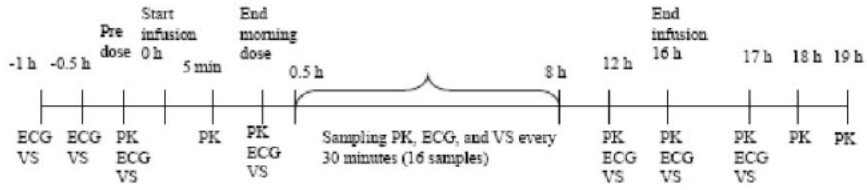
* Oral medication was not allowed within 3 hours of the start of infusion on the pharmacokinetic day.

† If oral medication was needed after the 16-hour infusion, final pharmacokinetic sample was taken prior to oral treatment. LC-IR, levodopa-carbidopa immediate release; PK, pharmacokinetic assessment; ECG, electrocardiogram; VS, vital sign assessment.

Treatment administration: Subjects remained on their established and individualized stable LCIG dose for the designated 16 hours of infusion on the two days of the study. The infusion duration was 16 hours on Day –1 and Day 1. The total dose per day of LCIG was composed of three individually adjusted doses: morning dose, continuous dose, and extra doses.

- The morning dose was administered by the pump to rapidly achieve the therapeutic dose level (within 10 to 30 minutes). The morning dose was expected to be 5 to 10 mL, corresponding to 100 to 200 mg levodopa; the morning dose was not to exceed 15 mL (300 mg levodopa). In the study, the morning dose ranged from 4 to 11.5 mL, corresponding to 80 to 230 mg levodopa.
- The continuous rate was to be kept within a range of 1 to 10 mL/hour (20 to 200 mg levodopa/hour) and was expected to be 2 to 6 mL/hour (40 to 120 mg levodopa/hour). In the study, the continuous rate ranged from 2.7 to 6.1 mL/hour (54 to 122 mg levodopa/hour).
- The extra doses were given if the patient became hypokinetic during the day. The extra dose was expected to normally be 0.5 to 2.0 mL. In the study, 13 subjects received extra doses. The extra doses ranged from 1 to 3 mL for all subjects except one subject who received an extra-dose of 5 mL. Use of extra doses of LCIG was discouraged during the PK sampling day. Only two subjects received extra doses on the PK assessment day.

None of the subjects who participated in the study were on LCIG for more than 16 hours a day. No rescue medications were administered

<table>
<tr><td></td><td>in this study.
<u>Diet:</u> On the PK sampling day, subjects fasted overnight (starting from 10:00 PM on the previous day). Subjects received standardized, low protein meals, starting with breakfast 2 hours after starting levodopa treatment, lunch and dinner. Water was taken ad libitum.</td></tr>
<tr><td>Study Population</td><td>19 patients were enrolled, and 18 patients completed the study. One patient was discontinued from the study due to non-compliance to the inclusion/exclusion criteria prior to dosing.
<u>Age:</u> 47-78 (65) years
<u>Gender</u>: 10 M/8 F
<u>Race</u>: 18 Caucasian.</td></tr>
<tr><td>Investigational Product</td><td>
<table>
<tr><th></th><th colspan="4">Regimen</th></tr>
<tr><td>Dosage Form</td><td>LCIG</td><td>LCIG, 100 mL</td><td>LCIG, 100 mL</td><td>LCIG, 100 mL</td></tr>
<tr><td>Strength
(Levodopa + Carbidopa)</td><td>20 mg/mL
+ 5 mg/mL</td><td>20 mg/mL
+ 5 mg/mL</td><td>20 mg/mL
+ 5 mg/mL</td><td>20 mg/mL
+ 5 mg/mL</td></tr>
<tr><td>Lot (Batch) Number</td><td>10H01G01</td><td>10F21G17</td><td>10B01G01</td><td>10C21G15</td></tr>
<tr><td>Potency (mg/mL), Levodopa</td><td>19.9</td><td>19.8</td><td>19.5</td><td>19.9</td></tr>
<tr><td>Potency (mg/mL), Carbidopa</td><td>4.98</td><td>4.99</td><td>4.99</td><td>4.94</td></tr>
<tr><td>Manufacturing Site</td><td colspan="4">(b) (4)</td></tr>
<tr><td>Manufacturing Date</td><td>01 August 2010</td><td>21 June 2010</td><td>01 February 2010</td><td>21 March 2010</td></tr>
<tr><td>Route of Administration</td><td>Infusion</td><td>Infusion</td><td>Infusion</td><td>Infusion</td></tr>
<tr><td>Expiration Date</td><td>01 August 2012</td><td>21 June 2012</td><td>01 February 2012</td><td>21 March 2012</td></tr>
</table>
Levodopa-carbidopa IR and continuous release (CR) tablets were commercially available and were provided to the subjects by the local pharmacy.</td></tr>
<tr><td>Sampling: Blood</td><td> 

VS = Vital Signs</td></tr>
<tr><td>Urine</td><td>none</td></tr>
<tr><td>Feces</td><td>none</td></tr>
<tr><td>Analysis</td><td>Sample analysis was carried out by (b) (4) using a validated HPLC with MS/MS detection between Aug 4 2010 and Nov 10 2010.
<table>
<tr><th></th><th>Carbidopa</th><th>Levodopa</th><th>3-O-Methyldopa</th></tr>
<tr><td>Matrix</td><td>Plasma</td><td>Plasma</td><td>Plasma</td></tr>
<tr><td>Method</td><td>LC/MS/MS</td><td>LC/MS/MS</td><td>LC/MS/MS</td></tr>
<tr><td>Linear Range (ng/ml)</td><td>0.5-250</td><td>10-5000</td><td>25 - 25000</td></tr>
<tr><td>LLOQ (ng/mL)</td><td>0.5</td><td>10</td><td>25</td></tr>
<tr><td>QCs</td><td>0.5,1.2, 3, 12, 40, 190 ng/mL</td><td>10, 24, 60, 240, 800, 3800 ng/mL</td><td>25, 90, 200, 815, 3000, 19000 ng/mL</td></tr>
<tr><td>Inter-run precision</td><td>3.7 -9.4%</td><td>5.1 – 9.5%</td><td>4 – 8.7%</td></tr>
</table></td></tr>
</table>

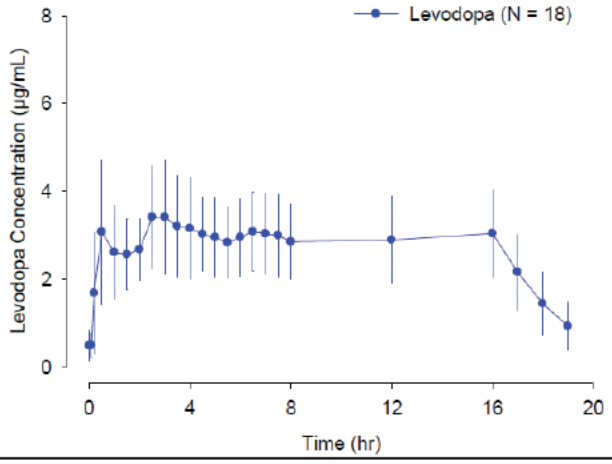
	Inter-run accuracy | -4.8 - 4 % | -4.3 – 1.5% | -1.9 – 6.7% Quality control assay validation is acceptable.
PK Assessment	The PK parameters of levodopa, 3-OMD and carbidopa were estimated using non-compartmental methods. These parameters included Cmax, Tmax, Cmin, Cavg, the apparent terminal phase elimination rate constant (β), t½, and AUC0-16, peak trough fluctuation (PTF) and dose-normalized PK parameters. AUC0-24 and CL/F were calculated for levodopa, and the metabolite to parent ratios (M/P) for Cmax and AUC0-16 were calculated for 3-OMD. The intra-subject coefficient of variation in the 2- to 16-hour infusion interval was also calculated.
Safety Assessment	Vital signs, orthostatic vital signs, ECG, Clinical laboratory, and AEs.
PD Assessment	none
Pharmacokinetic Results	The mean (SD) plasma concentration versus time profiles on linear scales for levodopa, 3-OMD, and carbidopa in LCIG are presented, respectively: **Figure 2. Mean Plasma Concentration versus Time Profiles of Levodopa with LCIG 16-hour Infusion, Linear Scale** 

Figure 4. **Mean Plasma Concentration versus Time Profiles of 3-OMD with LCIG 16-hour Infusion, Linear Scale**

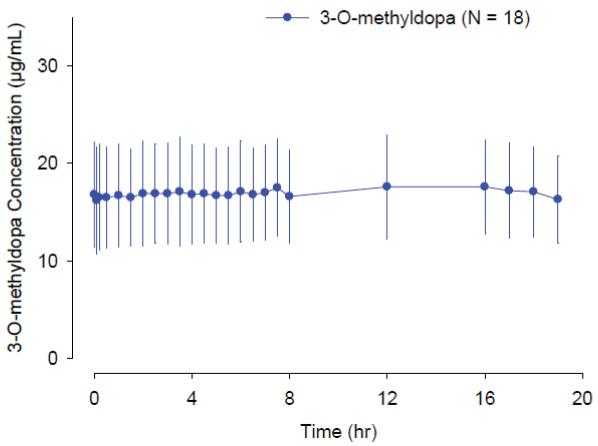
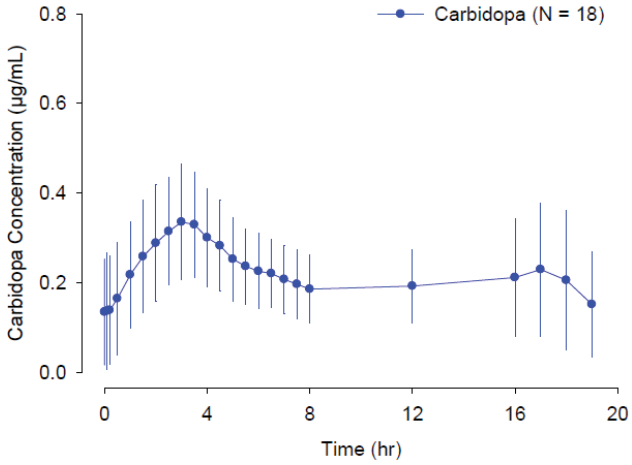


Figure 6. **Mean Plasma Concentration versus Time Profiles of Carbidopa with LCIG 16-hour Infusion, Linear Scale**



The mean ± SD PK parameters of levodopa, 3-OMD and carbidopa after administration of LCIG are presented below:

Table 7. Mean ± SD PK Parameters of Levodopa, 3-OMD and Carbidopa with LCIG 16-hour Infusion

Pharmacokinetic Parameters (units)		Analyte: Levodopa (N = 18)	3-OMD (N = 18)	Carbidopa (N = 18)
Total LCIG Dose (Day 1)	(mg)	1580 ± 403	--	395 ± 101
T_{max}	(h)	2.85 ± 2.31	8.38 ± 5.77	5.70 ± 5.22
C_{max}	(µg/mL)	4.21 ± 1.36	19.0 ± 5.66	0.371 ± 0.149
C_{min}	(µg/mL)	0.447 ± 0.282	15.1 ± 4.85	0.103 ± 0.0667
C_{avg}	(µg/mL)	2.91 ± 0.836	17.1 ± 4.99	0.221 ± 0.0834
AUC_{0-16}	(µg•h/mL)	46.5 ± 13.3	273 ± 79.8	3.54 ± 1.33
AUC_t	(µg•h/mL)	51.2 ± 14.9	316 ± 90.3	4.05 ± 1.65
AUC_{0-24}	(µg•h/mL)	53.8 ± 17.2[c]	--	--
$t_{½}$[a]	(h)	1.5 ± 0.19[c]	--	--
CL/F[b]	(L/h)	30.7 ± 7.52[c]	--	--
M/P (C_{max})	(%)	--	462 ± 82	--
M/P (AUC_{0-16})	(%)	--	597 ± 109	--
AUC_{0-16}/Dose	(ng•h/mL/mg)	29.7 ± 5.86	175 ± 40.2	9.22 ± 3.67
AUC_{0-24}/Dose	(ng•h/mL/mg)	34.3 ± 7.78[c]	--	--

a. Harmonic mean ± pseudo-standard deviation; evaluations of $t_{½}$ were based on statistical tests for β.
b. Parameter was not tested statistically.
c. N = 14.

Reviewer's comments: the median Tmax for Levodopa is 2.5 hours. The median Tmax for carbidopa is 3.5 hours.

The total variability in Cmax, Cmin, Cavg, AUC0-16 and AUC0-24 expressed as percent CV for levodopa, 3-OMD and carbidopa with LCIG 16-hour infusion are presented below:

Parameter	(Units)	Variability (%CV): Levodopa (N = 18)	3-OMD (N = 18)	Carbidopa (N = 18)
C_{max}	(µg/mL)	32	30	40
C_{min}	(µg/mL)	63	32	65
C_{avg}	(µg/mL)	29	29	38
AUC_{0-16}	(µg•h/mL)	29	29	38
AUC_{0-24}	(µg•h/mL)	32[a]	--	--
AUC_{0-16}/Dose	(ng•h/mL/mg)	20	23	40

a. N = 14.

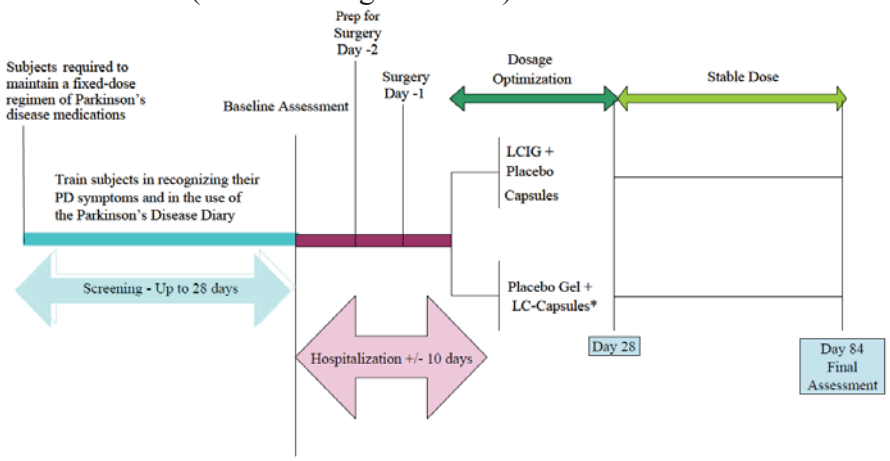
The inter- and intra-subject coefficients of variation (and 95% confidence interval for coefficients of variation) for the 2- to 16-hour interval relative to start of LCIG infusion is presented below:

	<table><tr><th rowspan="2">Analyte[a]</th><th rowspan="2">Number of Subjects</th><th colspan="2">Inter-subject</th><th colspan="2">Intra-subject</th></tr><tr><th>CV (%)</th><th>95% Confidence Interval</th><th>CV (%)</th><th>95% Confidence Interval</th></tr><tr><td>Levodopa</td><td>18</td><td>32</td><td>18 – 42</td><td>13</td><td>12 – 15</td></tr><tr><td>3-OMD</td><td>18</td><td>33</td><td>18 – 43</td><td>6</td><td>5 – 6</td></tr><tr><td>Carbidopa</td><td>18</td><td>40</td><td>22 – 53</td><td>19</td><td>17 – 21</td></tr></table> a. Time interval is from 2 to 16 hours. Note: Estimates are made on a linear mixed model for log concentration with time as a fixed and repeated effect with compound symmetric covariance.
Safety	There was no SAE or death in the study.
Conclusion	The average total daily LCIG dose was 1580 mg for levodopa and 395 mg for carbidopa on the PK assessment day of the study. Following 16-hour infusion of LCIG, peak plasma levels of levodopa is reached at median Tmax of 2.5 hours, and maintained consistent levodopa levels over the course of infusion. Following termination of infusion at night, levodopa levels declined rapidly with t1/2 of 1.5 hours. The within-subject coefficient of variation in levodopa, 3-OMD and carbidopa concentrations over the 2 to 16 hours time interval relative to starting LCIG infusion was low (13%, 6% and 19%, respectively).

PK Results in Phase 3 Study:

Study S187-3-001/002	A randomized, double-blind, double-dummy, efficacy, safety, and tolerability study of levodopa-carbidopa intestinal gel in levodopa-responsive Parkinson's subjects receiving optimized treatments with Parkinson medicinal products who continue to experience persistent motor fluctuations.
PK Objective	To evaluate the pharmacokinetics of levodopa following administration of LCIG. (Please refer to Dr. Hongshan Li's PM review) To summarize the pharmacokinetic results for hydrazine, (b) (4) and (b) (4) as well as the parent compound carbidopa with LCIG infusion or LC-oral administration in Levodopa-Responsive subjects with advanced Parkinson's disease.
Study design and Dose Administration	Study S187-3-001 and Study S187-3-002 were 2 identically-designed, Phase 3, 12-week, randomized, double-blind, double-dummy, parallel-group, multicenter studies recruiting subjects from distinct sites. There were two treatment arms in these two studies. Subjects eligible for the studies were administered a gel infusion via a pump and oral capsules. The gel was delivered via a Percutaneous Endoscopic Gastrostomy with Jejunal extension tube (PEG-J). With few exceptions, all other anti-PD medications that the subjects were taking were continued at their pre-randomization doses; including dopamine-agonists, catechol-O-methyl transferase (COMT)-inhibitors, MAO-B inhibitors, and

amantadine. The exceptions were apomorphine and levodopa formulations containing peripheral decarboxylase inhibitors other than carbidopa in an immediate release (IR) (4:1 ratio). Subjects taking any other formulations were converted to treatment with the (IR) formulation of levodopa/carbidopa (4:1) at least 28 days prior to randomization. (Please see figure below).



* Levodopa-Carbidopa IR tablets, encapsulated.

Subjects were randomized to treatment at an individualized dose for up to 12 weeks in 1 of 2 treatment groups:

- LCIG group: Levodopa-Carbidopa Intestinal Gel (levodopa, 20 mg/mL and carbidopa, 5 mg/mL) and placebo capsules.

Or

- LC-oral group: Placebo intestinal gel and oral levodopa-carbidopa (levodopa, 100 mg and carbidopa, 25 mg) IR capsules.

The total daily dose of infusion (LCIG or placebo gel) was composed of 2 components, the morning dose and the continuous maintenance infusion dose, administered over a full 16-hour period. At night, after disconnecting the pump, the tubing was to be flushed with potable water.

A morning dose was administered as a bolus infusion by the pump to fill the dead space of the intestinal tube and rapidly achieve a therapeutic dose level (over approximately 10 to 30 minutes). This was usually 5 to 10 mL and corresponded to 100 to 200 mg of levodopa. The total morning dose was not to exceed 15 mL (300 mg levodopa).

Calculation of continuous dose (16-hour day):

- Total oral daily dose minus morning dose and last dose of the day = continuous dose over 16 hours
- Continuous dose divided by 16 hours = continuous hourly

<table>
<tr><td></td><td>dose.
Subjects in both treatment arms were allowed to take rescue doses of oral open-label levodopa-carbidopa 100/25 mg IR whole or ¾ tablets (L-C rescue tablets), as needed, to address immediate serious medical needs, such as the rapid deterioration of motor symptoms.

During assessment days, rescue doses of levodopa-carbidopa tablets were to be avoided, if at all possible, due to their potential impact on efficacy measures. During the final assessment days at the end of the 12-week double-blind period, no rescue medication was to be taken unless required to address immediate serious medical needs.

Subjects randomized into the study were to have been on optimized oral levodopa-carbidopa IR. After randomization to the equivalent LCIG dose (with placebo capsules) or LC-oral dose capsules (with placebo gel), the subjects were maintained on their previously established stable regimen of antiparkinsonian medications. For example, if a subject was receiving an oral dose every 3 hours, then the subject was to remain on that same schedule of oral double-blind medication.</td></tr>
<tr><td>Study Population</td><td>Data on all four compounds of interest were available from 16 subjects. Disposition of the 16 subjects who underwent PK sampling is summarized in the table below:<table><tr><th>Study</th><th>LCIG</th><th>LC-oral</th></tr><tr><td>S187.3.001</td><td>N = 6</td><td>N = 3</td></tr><tr><td>S187.3.002</td><td>N = 5</td><td>N = 2</td></tr><tr><td>Total</td><td>N = 11</td><td>N = 5</td></tr></table></td></tr>
<tr><td>Sampling: Blood</td><td>On Study Days 42 and 43, a series of whole blood samples were to be collected for evaluation of plasma concentrations of levodopa, its metabolite 3-O-methyldopa (3-OMD), carbidopa, and possible carbidopa metabolites.

Under Amendment 7 of Study S187.3.001 and Amendment 3 of Study S187.3.002, blood samples for determination of levodopa, carbidopa, 3-OMD, (b) (4) (b) (4) and hydrazine concentrations were collected on Study Days 42 at 12 and 16 hours post-infusion initiation and on Study Day 43 prior to initiation of intestinal gel infusion and after start of infusion at the following time points: 1, 2, 4, and 8 hours.</td></tr>
</table>

Figure 3. **Vital Sign Measurements, ECG Collection, and Pharmacokinetic Sampling Schedule, First Day**

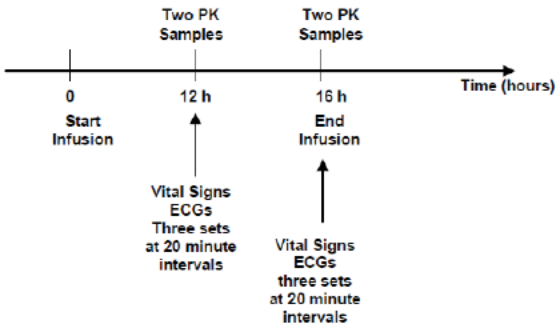
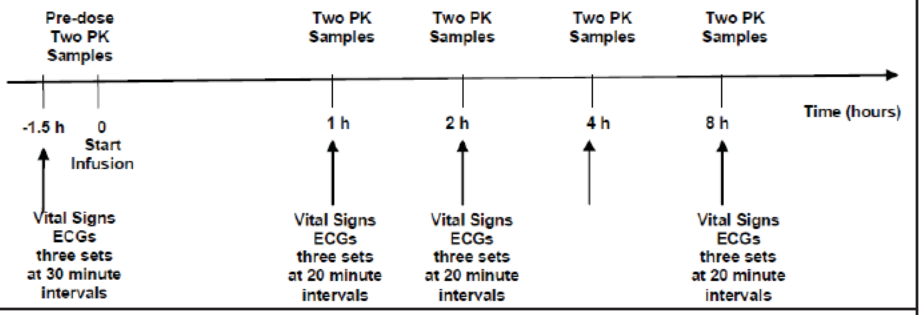


Figure 4. **Vital Sign Measurements, ECG Collection, and Pharmacokinetic Sampling Schedule, Second Day**



Urine	none
Feces	none
Analysis	Plasma concentrations of levodopa, 3-O-Methyldopa, carbidopa were determined at [redacted] (b) (4) using a validated liquid chromatography with tandem mass spectrometry method. Plasma concentrations of hydrazine, [redacted] (b) (4) and [redacted] (b) (4) were determined at the Drug Analysis Department, Abbott Laboratories, using a validated liquid chromatography with tandem mass spectrometry method.

	Hydrazine	[redacted] (b) (4)	[redacted] (b) (4)
Method	Salt-assisted LC/MS/MS	Protein Precipitation Extraction LC/MS/MS	Protein Precipitation Extraction LC/MS/MS
Linear Range (ng/ml)	[redacted] (b) (4)		
LLOQ (ng/ml)			
QCs (ng/ml)			
Inter-assay precision			
Inter-assay accuracy			

<table>
<tr><td></td><td>
<table>
<tr><th></th><th>Carbidopa</th><th>Levodopa</th><th>3-O-Methyldopa</th></tr>
<tr><td>Matrix</td><td>Plasma</td><td>Plasma</td><td>Plasma</td></tr>
<tr><td>Method</td><td>LC/MS/MS</td><td>LC/MS/MS</td><td>LC/MS/MS</td></tr>
<tr><td>Linear Range (ng/ml)</td><td>10 - 5000</td><td>10-5000</td><td>400 - 25000</td></tr>
<tr><td>LLOQ (ng/mL)</td><td>10</td><td>10</td><td>400</td></tr>
<tr><td>QCs</td><td>24, 60, 240, 800, 3800 ng/mL</td><td>24, 60, 240, 800, 3800 ng/mL</td><td>800, 1500, 3000, 7000, 19000 ng/mL</td></tr>
<tr><td>Inter-run precision</td><td>2.9 -7.8%</td><td>3.8 – 10%</td><td>2.4 – 5.1%</td></tr>
<tr><td>Inter-run accuracy</td><td>-3.4 – 6.1 %</td><td>-5.3 – 4.5%</td><td>-4.6 – 4.5%</td></tr>
</table>
Quality control assay validation is acceptable
</td></tr>
<tr><td>PK Assessment</td><td>population pharmacokineticsanalysis for levodopa (please refer to Dr. Hongshan Li's PM review). Plasma concentration of carbidopa, hydrazine, (b) (4) and (b) (4) were summarized. When measurable plasma concentrations were found, the AUC0-16 values were calculated using the pre-dose (0 hour), 1, 2, 4, 8 hour samples from Study Day 43 and the 12, 16 hour on Study Day 42.</td></tr>
<tr><td>Pharmacokinetic Results</td><td>For PK results of levodopa, please refer to Dr. Hongshan Li's PM review.

Among the 11 subjects randomized to LCIG, dosing records were available for nine subjects on the first PK sampling day (Study Day 42) and for eight subjects on the second PK sampling day (Study Day 43).The mean ² SD total levodopa daily doses were 1284 ² 342 mg on the first PK sampling day and 1307 ² 364 mg on the second PK sampling day. The mean ² SD total carbidopa daily doses were 321 ² 86 mg on the first PK sampling day and 327 ² 91 mg on the second PK sampling day.

Among the five subjects randomized to LC-oral, dosing records were available for four subjects on each of the two PK sampling days. The mean ² SD total levodopa daily doses were 1325 ² 838 mg on both PK sampling days. The mean ² SD total carbidopa daily doses were 331 ² 210 mg on both PK sampling days.

The total daily doses of levodopa/carbidopa were comparable for subjects treated with LCIG and LC-oral.

<u>Hydrozine Plasma Exposure</u>:
Ten of 11 subjects treated with LCIG and three of five subjects treated with LC-oral did not have measurable hydrazine levels in plasma (less than the LLOQ of (b) (4) ng/mL). Only one subject (Subject 111-102) treated with LCIG showed measurable levels of hydrazine (in the 1, 2, 4, 8, 12 hour samples) with hydrazine concentrations ranging from (b) (4) ng/mL. The hydrazine AUC0-16 for this subject was (b) (4) ng.hr/mL.</td></tr>
</table>

Two subjects treated with LC-oral showed measurable hydrazine concentrations only once in the 16 hour interval ([(b) (4)] ng/mL at 4 hr for one subject and [(b) (4)] ng/mL at 8 hr for the other subject).

Carbidopa, [(b) (4)] and [(b) (4)] Plasma Exposures:

Ten of 11 subjects treated with LCIG and all five subjects on LC-oral did not have measurable [(b) (4)] levels (less than LLOQ of [(b) (4)] ng/mL). Only one subject treated with LCIG showed a measurable concentration of [(b) (4)] ng/mL 16-hr post dosing, which is close to the LLOQ (Subject 136-102).

[(b) (4)] exposure over the 16 hours of infusion (AUC0-16) with LCIG is less than [(b) (4)] ng.hr/mL (calculated as [(b) (4)] ng/mL LLOQ *16 hr). Therefore, exposure (AUC0-16) of [(b) (4)] in subjects treated with LCIG is less than [(b) (4)]% of that of carbidopa. Similarly, exposure (AUC0-16) of [(b) (4)] in subjects treated with LC-oral is less than [(b) (4)]% of that of carbidopa.

Four of 11 subjects treated with LCIG and one of five subjects treated with LC-oral did not have measurable [(b) (4)] levels (less than LLOQ of ~ [(b) (4)] ng/mL). Seven subjects treated with the LCIG and four subjects treated with LC-oral showed measurable concentrations in one or more samples. With LCIG administration, the measurable [(b) (4)] levels ranged from [(b) (4)] to [(b) (4)] ng/mL; with LC-oral administration, the measurable [(b) (4)] levels ranged from [(b) (4)] ng/mL.

The AUC0-16 individual and mean values of [(b) (4)] and the ratios of [(b) (4)] to carbidopa AUC0-16 are summarized in tables below:

Table 2. [(b) (4)] AUC_{0-16} Individual Values and Summary Statistics for Subjects Treated with LCIG

Subject	[(b) (4)] AUC_{0-16} (ng•hr/mL)	Carbidopa AUC_{0-16} (ng•hr/mL)	AUC Ratio [(b) (4)] Carbidopa
103102	[(b) (4)]		[(b) (4)]
107110			
107111			
107112			
111102			
126103			
127109			
127110			
136102			
148101			
149103			
N	7	11	7
Mean	[(b) (4)]	3380	[(b) (4)]
SD		1080	
Min		1500	
Median		3310	
Max		5170	
CV%		32	

NM = Non-measurable concentrations; for subjects with measurable concentrations at some time points, non-measurable concentrations were imputed with zero for calculation of AUC

Table 3. [redacted] AUC_{0-16} Individual Values and Summary Statistics for Subjects Treated with Oral Levodopa/Carbidopa (LC-oral)

Subject	[redacted] AUC_{0-16} (ng•hr/mL)	Carbidopa AUC_{0-16} (ng•hr/mL)	[redacted] AUC Ratio Carbidopa
107114	[redacted]		
127107			
144101			
146105			
149104			
N	4	5	4
Mean	[redacted]	3460	[redacted]
SD		1970	
Min		1080	
Median		3830	
Max		5850	
CV%		57	

NM = Non-measurable concentrations; for subjects with measurable concentrations at some time points, non-measurable concentrations were imputed with zero for calculation of AUC

Reviewer's comments: Hydrazine is a degradation product of carbidopa in LCIG that is a known toxicant (e.g., its effect of carcinogenicity and genotoxicity) [redacted]

One subject with LCIG had detectable levels (in 5 out of 7 samples) of hydrazine, measurable hydrazine concentrations ranged from [redacted] ng/mL (value of AUC 0-16 was [redacted] ng.hr/mL). Two of 5 subjects treated with LC-oral showed measurable hydrazine concentrations [redacted] and [redacted] ng/mL) only at 1 time point in the 16-hour sampling interval. The high level of hydrazine due to carbidopa degradation in LCIG is observed and anticipated.

[redacted] (and possibly [redacted]) is a metabolite of carbidopa. After oral administration of CD/LD, [redacted] is below the level of quantification, and the median Tmax of [redacted] is greater than that of CD (6 hr vs., 1.5 hr); which indicates [redacted] as a metabolite is formed by CD in the system. After LCIG administration, however, while majority of [redacted] is below the level of quantification, the median Tmax of [redacted] is less than that of CD (1 hr vs., 2 hr), indicating that the [redacted] as a degradant impurity from LCIG is formed and absorbed along with CD from LCIG.

	(b) (4)

Appendix 2: PHARMCOMETRIC REVIEW

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

NDA Number	203952
Drug Name	Levodopa-Carbidopa Intestinal Gel (LCIG)
Pharmacometrics Reviewer	Hongshan Li, Ph.D.
Secondary Pharmacometrics Reviewer	Atul Bhattaram, Ph.D.
Sponsors	AbbVie Inc.

1 PERTINENT REGULATORY BACKGROUND

LCIG is a formulation of levodopa and carbidopa delivered from a medication cassette reservoir via the CADD-Legacy® 1400 portable infusion pump into the proximal small intestine through a percutaneous endoscopic gastrostomy with jejunal extension (PEG-J). LCIG is a combination of levodopa and carbidopa, indicated for the long-term treatment of motor fluctuations in patients with advanced (b) (4) Parkinson's disease (b) (4) As a 505(b)(2) application, this NDA references Sinemet® (NDA 017555) for efficacy and safety. The US clinical development program for the LCIG System was initiated in 2008 with dosing of the first subject in Study S187-3-004. Key communications between the sponsor and the FDA are briefly summarized below:

- On18 January 2000LCIG was granted orphan drug designation for the treatment of advanced PD (Designation Number 99-1294).
- On 30 October 2002, the Agency informed the sponsor that submission of safety data on at least 300 patients for 6 months and 100 patients for 12 months would be necessary to meet the requirements for long-term safety exposure.
- On 15 November 2011, the Agency agreed that the LCIG System is considered a combination product (drug, pump, and tubing). A Master Access File (MAF) for the Smiths Medical pump used with LCIG has been submitted, according to *Guidance for Industry and FDA Staff Total Product Life Cycle: Infusion Pump - Premarket Notification [510(k)] Submissions*. Tubing components that are required to administer LCIG will be filed as Premarket Notification 510(k) applications submitted to the Center for Devices and Radiological Health. The LCIG System elements will be cross-labeled to ensure control of its component parts. In addition, there are tubing components currently approved within the US that are compatible with the LCIG System. These tubing components are listed in the proposed US Package Insert for the product and compatibility data are provided in Module 3, Section 3.2.P.2.4 and Section 3.2.P.2.6.
- On 16 November 2012, the sponsor submitted LCIG (NDA 203952) to the FDA. On 15 January 2013, the NDA was issued a reject to file letter to the sponsor under 21 CFR 314.101(d), after a preliminary review. The FDA found the application is not sufficiently complete to permit a substantive review due to the lack of information for chemistry, statistics and clinical trials.
- A Type A Meeting was held between the FDA and the sponsor to discuss the RTF on

March 14 2013. There were 33 questions were discussed about the RTF.

- On 23 May 2014, the sponsor resubmitted LCIG (NDA 203952). The resubmission addresses deficiencies that were set forth in the RTF letter. Section 1.2 of this application has detailed description of how AbbVie addressed each item cited within the RTF letter.

2 RESULTS OF SPONSOR'S ANALYSIS

2.1 Sponsor's Population Pharmacokinetics analysis

Title of Study: Population Pharmacokinetics of Levodopa Following Jejunal Administration of Levodopa-Carbidopa Intestinal Gel or Oral Administration of Levodopa-Carbidopa Capsules to Subjects with Advanced Parkinson's Disease–Analyses of Data From LCIG Phase 1 and 3 Studies

Objective: To characterize the population pharmacokinetics of levodopa following jejunal administration of levodopa-carbidopa intestinal gel (LCIG) or oral administration of levodopa-carbidopa (LC-oral) capsules to subjects with advanced Parkinson's disease using the data from LCIG Phase 1 and 3 studies.

Methodology: A nonlinear mixed-effects model was developed to characterize the pharmacokinetics of levodopa with LCIG or LC-oral administration using available data from Studies S187-1-002 and S187-3-001/S187-3-002. Covariates that accounted for variability in levodopa pharmacokinetics were determined and the relationships between covariates and levodopa exposure were quantified. The final model underwent internal evaluation using non-parametric bootstrap and visual predictive check. The model also underwent external evaluation by characterizing the ability of the model to predict the pharmacokinetic data from Study S187-3-004, a study that was not utilized in the model development. The non-linear mixed-effects modeling software NONMEM was used for data analysis and simulations.

Study Subjects: Sixty-eight male and female subjects with advanced Parkinson's disease who participated in Studies S187-1-002 and S187-3-001/S187-3-002 and who had available pharmacokinetic data and dosing history information (recorded) during the pharmacokinetic sampling study days were included in the model development. Of the 68 subjects, 45 subjects received LCIG and 23 subjects received LC-oral. Adult male and female subjects (N = 311) with advanced Parkinson's disease who participated in Study S187-31-004 and who had plasma concentration and dosing history information (recorded or imputed) during the pharmacokinetic sampling study days were included in the model external evaluation using stochastic simulations.

Criteria for Evaluation

Model Development: Population pharmacokinetic analyses were performed using the actual sampling times relative to dosing. Pharmacokinetic models were built using a nonlinear mixed-effects modeling approach with NONMEM software. The first-order conditional estimation (FOCE) method with interaction between inter-subject variability and residual variability was used throughout the model building process. A user defined NONMEM subroutine (ADVAN 6) was used for model development. One- and two-compartment models were evaluated as starting models and complexity was added to the model in a stepwise manner. Several criteria were used to evaluate the improvement in the model performance and to select the final model. The Likelihood Ratio Test was used for comparing rival hierarchical models where a decrease in NONMEM objective function value (–2 log likelihood) of 7.88 points was necessary to consider the improvement in model performance statistically significant at $\alpha = 0.005$ and 1 degree of

freedom. The Akaike information criterion (AIC) was used for comparing rival non- hierarchical models. Other selection criteria used included improved goodness of fit and residual plots, increased precision in parameter estimation and reduced variance of inter-subject and residual errors.

Covariates investigated for influence on pharmacokinetic parameters included: body weight (WT), age, sex, concomitant use of the catechol-O-methyl transferase (COMT)-inhibitor entacapone and treatment (LCIG versus LC-oral).

Model Internal Evaluation: To assess robustness of the final model and to estimate confidence intervals of the model parameters, 1000 bootstrap datasets were constructed by randomly sampling (with replacement) from the original dataset. Model parameters were estimated for each bootstrap replicate and the resulting values were used to calculate medians and confidence intervals.

To assess the ability of the model to replicate the data from which it was built in simulations, the final model parameters were used to simulate 500 replicates of the observed data. Levodopa concentrations were categorized by rounded time after dosing. Subsequently, the observed concentrations and calculated statistics [median, 5^{th} percentile (P5) and 95^{th} percentile (P95)] of observed concentrations were compared graphically to the 95% confidence intervals for the median, P5 and P95 of simulated concentrations. The 95% confidence intervals for the median, P5 and P95 of simulated concentrations were calculated from the 2.5^{th} percentile and 97.5^{th} percentiles of each parameter across simulated replicates.

Model External Evaluation: To assess the ability of the model to adequately predict levodopa plasma concentrations for a study of LCIG that was not utilized in model development, the final model parameters were used to simulate 500 replicates of Study S187-3-004 pharmacokinetic data. For calculation of summary statistics and graphical display of observed and simulated data for Study S187-3-004, concentration data were categorized by rounded time relative to start of morning infusion of LCIG. Subsequently, the observed concentrations, as well as calculated statistics (median, P5 and P95) of observed concentrations were compared graphically to the 95% confidence intervals for the median, P5 and P95 of simulated concentrations. The 95% confidence intervals for the median, P5 and P95 of simulated concentrations were calculated from the 2.5^{th} percentile and 97.5^{th} percentile of each parameter across simulated replicates.

Results: The final levodopa population pharmacokinetic model was a two-compartment model with a transit compartment for absorption, first-order elimination, bioavailability for LCIG relative to LC-oral, different first-order transit absorption rate constants for LCIG versus LC-oral and different residual (intra-subject) variability for LCIG versus LC-oral. Inter-subject variability was estimated for CL, Vc and K_{TR} using exponential models. The residual variability was estimated using a combined additive and proportional error models. Body weight was a statistically significant covariate for the volume of the central compartment (volume of the central compartment allometrically scaled on body weight with an exponent of 1). Levodopa clearance was not found to be statistically significantly correlated with body weight or sex of the subject ($p > 0.01$). Additionally, no statistically significant relationship was found between concomitant use of the catechol-O-methyl transferase, entacapone and levodopa clearance. The estimated pharmacokinetic parameters and their associated variability for the final model are presented below:

Parameter		Point Estimate (%RSE)[a]	Bootstrap Median [95 % CI][b]
K_{TR} (hr^{-1})	LCIG	9.2 (19)	9.7 [6.0 to 14.3]
	LC-oral	2.4 (30)	2.2 [0.85 to 5.2]
CL/F (L/hr)		24.8 (5)	24.4 [20.4 to 26.8]
Vc/F (L)		58.5 (11) *WT(kg)/70	56.0 [36.6 to 71.0] * WT(kg)/70
Q/F (L/hr)		6.8 (22)	7.9 [4.1 to 17.2]
Vp/F (L)		72.9 (49)	80.3 [22.9 to 407.8]
F_{rel}	LCIG	0.97 (1)	0.97 [0.95 to 0.98]
	LC-oral	1 Fixed	1 Fixed
ω^2_{KTR}		0.78 (31)	0.62 [0.13 –1.3]
ω^2_{CL}		0.11 (17)	0.11 [0.07 to 0.15]
ω^2_{Vc}		0.37 (40)	0.33 [0.09 to 0.94]
$\omega^2_{KTR,CL}$		–0.14 (31)	–0.11 [–0.23 to –0.005]
σ^2		0.03 (30)	0.02 [0.008 to 0.05]
LC-oral		0.09 (28)	0.09 [0.000001 to 0.13]
σ^2		0.09 (39)	0.08 [0.005 to 0.20]
LC-oral		0.34 (30)	0.35 [0.09 to 0.66]

Notes: CI = confidence interval, K_{TR} = first-order absorption transit rate constant, CL/F = apparent clearance, Q/F = apparent inter-compartmental clearance; Vc/F = apparent volume of central compartment;
Vp/F = apparent volume of peripheral compartment; F_{rel} = bioavailability for LCIG relative to LC-oral;
ω^2 variance of intersubject variability; σ^2 variance of residual variability

a. NONMEM point estimate and the associated % relative standard error (% RSE).

b. The median and 95% confidence interval (2.5^{th} and 97.5^{th} percentiles) calculated from the parameter estimates of the successfully converging runs (977) of the 1000 bootstrap datasets.

Results (Continued): The developed levodopa population pharmacokinetic model was robust and replicated the features of the data from which it was built in simulations. In addition, the model performed well in external evaluation and was able to adequately predict levodopa plasma concentrations for a study of LCIG that was not utilized in model development.

Conclusions: A population model for levodopa pharmacokinetics from Levodopa-Carbidopa Intestinal Gel (LCIG) and oral levodopa-carbidopa immediate release formulation (over-encapsulated sinemet, LC-oral) was developed using available data from Studies S187-1-002 and S187-3-001/S187-3-002. The final model underwent internal evaluation using the data from the above studies and external evaluation using available pharmacokinetic data from Study S187-3-004. The final levodopa population pharmacokinetic model was a two-compartment model with a transit compartment for absorption, first-order elimination, bioavailability for LCIG relative to LC-oral, different first-order transit absorption rate constants for LCIG versus LC-oral and different residual (intra-subject) variability for LCIG versus LC-oral. Inter-subject variability was estimated for CL, Vc and K_{TR} using exponential models. The residual variability was estimated using a combined additive and proportional error models. Body weight was a statistically significant covariate for the volume of the central compartment (volume of the central compartment allometrically scaled on body weight with an exponent of 1). Levodopa clearance was not found to be statistically significantly correlated with body-weigh or sex of the subject ($p > 0.01$). Additionally, no statistically significant relationship was found between concomitant use of catechol-O-methyl transferase, entacapone, and levodopa clearance. Age almost reached significance for inclusion as a covariate for levodopa clearance (p=0.0057). The

model estimated apparent clearance (CL/F) of levodopa, when co-administered with carbidopa, was 24.8 L/h in subjects with advanced Parkinson's disease. The apparent steady-state volume of distribution (V_{SS}/F) of levodopa was approximately 130 L for a 70 kg subject. LCIG showed comparable bioavailability to LC-oral with estimated relative bioavailability of 97% (95% bootstrap confidence interval of 95% to 98%). LCIG was absorbed faster than LC-oral, which is consistent with delivery of levodopa/carbidopa directly to the jejunum with LCIG. The first-order absorption transit rate constant was estimated to be 9.2 hr^{-1} for LCIG and 2.4 hr^{-1} for LC-oral. The inter-subject variability was estimated to be 88% for the absorption transit rate constant, 33% for levodopa apparent clearance and 60% for levodopa central volume of distribution. Administration of LCIG was estimated to be associated with approximately half the intra-subject variability in levodopa concentrations compared to administration of LC-oral in subjects with advanced Parkinson's disease. The estimated proportional residual error (first component of intra-subject variability) was 15% for LCIG versus 29% for LC-oral. The estimated standard deviation of the additive residual error in levodopa concentrations (second component of intra-subject variability) was 0.3 µg/mL for LCIG versus 0.59 µg/mL for LC-oral.

The developed levodopa population pharmacokinetic model was robust and replicated the features of the data from which it was built in simulations. In addition, the model performed well in external evaluation and was able to adequately predict levodopa plasma concentrations for a study of LCIG that was not utilized in model development.

FDA Reviewer's Comments: The population pharmacokinetics analysis was based on levodopa concentration data from the Phase I study S187-1-002 and Phase III studies S187-3-001/S187-3-002. For model evaluation, the model was successfully applied to levodopa concentration data of Phase III study S187-3-004. This population pharmacokinetics analysis had two merits:

- *It obtained the bioavailability of levodopa in LCIG relative to levodopa in the oral formulation, which was 97%.*
- *It compared the intra-subject variability of levodopa between LCIG and the oral formulation.*

The clinical questions were addressed by population pharmacokinetics approach instead of dedicated studies. Please refer to the **QUESTION BASED REVIEW (QBR)** *for more discussion on the implications of findings from population pharmacokinetic analysis.*

3 FDA REVIEWER'S ANALYSIS

The reviewer was able to assess the population pharmacokinetic analysis and agrees with the findings as reported.

4 SPONSOR'S ANALYSIS DATA AND FILES

Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
Model21.ctl.txt	Population pharmacokinetic model	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\LevodopaCarbidopaIntestinalGel_NDA203952_HL\pop PK analysis

	(Final)	
model21-out.txt	Output of final population pharmacokinetic model	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\LevodopaCarbidopaIntestinalGel_NDA203952_HL\pop PK analysis
LCIG_1002_3001_3002_PK_SIM_09AUG12_V02.CSV	Population pharmacokinetic dataset	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\LevodopaCarbidopaIntestinalGel_NDA203952_HL\sponsor's data and reports

5 REFERENCES

Pappert EJ, Lipton JW, Goetz CG, Ling ZD, Stebbins GT, Carvey PM. The stability of carbidopa in solution. Mov Disord. 1997 12(4):608-10.

Cedarbaum JM. Stability of levodopa/carbidopa solutions. Mov Disord. 1997 12(4):625.

6 APPENDIX: Individual mean daily levodopa dose (mg) data for the patients of Studies s187.3001 and s187.3002 at maintenance period (Study Weeks 5-12)

ID	Morning	Flow Rate	Pump	Rescue	Night	Unclassified	Total
S187.3.001-101-102	[redacted] (b) (4)						
S187.3.001-107-101							
S187.3.001-107-110							
S187.3.001-107-111							
S187.3.001-107-112							
S187.3.001-126-102							
S187.3.001-126-103							
S187.3.001-130-102							
S187.3.001-148-101							
S187.3.001-149-101							
S187.3.001-149-103							
S187.3.001-436-002							
S187.3.001-436-103							
S187.3.001-436-104							
S187.3.001-437-001							
S187.3.001-439-001							
S187.3.001-446-102							
S187.3.002-103-102							
S187.3.002-104-102							
S187.3.002-104-105							
S187.3.002-104-107							
S187.3.002-104-109							
S187.3.002-111-102							
S187.3.002-114-102							
S187.3.002-115-102							
S187.3.002-119-101							
S187.3.002-119-105							
S187.3.002-127-102							
S187.3.002-127-106							
S187.3.002-127-109							
S187.3.002-127-110							
S187.3.002-136-101							
S187.3.002-136-102							
S187.3.002-146-101							
S187.3.002-213-101							
Average	135	951	1146	116	124	285	1181
SD	59	462	478	54	67	240	480
Minimum	0	414	604	50	50	50	631
Quartile 1	100	669	824	75	75	100	907
Median	160	854	1022	100	100	200	1031
Quartile 3	160	1070	1245	146	167	450	1278
Maximum	274	2738	2935	267	300	800	2942
Source: sponsor's dataset "ex30012.xpt" for Studies s187.3001/s187.3002.							

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BEI YU
02/28/2014

HONGSHAN LI
02/28/2014

VENKATESH A BHATTARAM
02/28/2014

YUXIN MEN
02/28/2014

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 203952	**Reviewer:** Kelly M. Kitchens, Ph.D.	
Submission Date:	May 28, 2013		
Division:	Division of Neurology Products	**Team Leader:** Angelica Dorantes, Ph.D.	
Applicant:	AbbVie Inc.	**Acting Supervisor:** Richard Lostritto, Ph.D.	
Trade Name:	Duopa	**Date Assigned:**	May 30, 2013
Established Name:	Levodopa-Carbidopa Intestinal Gel	**Date of Review:**	October 8, 2013
Indication:	Long-term treatment of motor fluctuations in patients with advanced (b) (4) Parkinson's disease (b) (4)	**Type of Submission:** 505 (b)(2) NDA Resubmission after RTF	
Formulation/ strengths	Intestinal Gel/ 20 mg/mL and 5 mg/mL		
Route of Administration	PEG-J		
Type of Review:	Dissolution Method and acceptance criteria		

SUMMARY:

Submission:

The Applicant submitted NDA 203952 per section 505(b)(2) for Lovodopa-Carbidopa Intestinal Gel (LCIG). The 505(b)(2) application relies upon studies conducted by the Applicant to support approval, as well as the FDA's previous finding of safety and effectiveness for Sinemet® (carbidopa and levodopa) Oral Tablets manufactured by Merck and Co. and approved under NDA 17555 on May 2, 1975. LCIG (20 mg/mL levodopa, 5 mg/mL carbidopa monohydrate) is indicated for the long-term treatment of motor fluctuations in patients with advanced (b) (4) Parkinson's disease (b) (4)

The current NDA was originally submitted on November 16, 2012 by AbbVie Inc. However, on January 15, 2013, a refuse-to-file (RTF) letter was issued for this NDA due to various CMC, statistical, and clinical issues. Therefore, the current submission dated May 28, 2013, is a resubmission of NDA 203952 addressing all of the deficiencies identified in the RTF letter.

Biopharmaceutics Information:
Although the Applicant conducted dissolution tests to confirm the [redacted] dissolution of the LCIG drug product and the dissolution profiles for these tests were included in the current submission, the Applicant stated that [redacted]

Therefore, the dissolution method development and the data supporting its discriminating ability were not submitted, and the dissolution test and its acceptance criteria were NOT included in the specifications table of the drug product.

Reviewer's Initial Assessment:
The Applicant's reasons for not performing dissolution testing were considered unacceptable and the following potential review issues were communicated to the Applicant on July 1, 2013:

1. *Your statement and rationale for concluding [redacted] of LCIG drug product performance are not acceptable. According to 21 CFR 314.50, every drug product application must include the specifications necessary to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product, including, and acceptance criteria relating to, dissolution rate. Therefore, conduct dissolution testing for both components of your proposed drug product using an adequate dissolution method. The proposed dissolution method should be supported by the following information/data:*
   a. *Solubility data for the drug substance covering the pH range;*
   b. *Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product. If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least [redacted]% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable;*
   c. *Provide the complete dissolution profile data (individual, mean, SD, profiles) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim);*
   d. *Data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the*

reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables).

2. *For the selection of the dissolution acceptance criterion of your product, the following points should be considered:*
   a. *Normally, the dissolution profile data from the pivotal clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criterion of your product (i.e., specification-sampling time point and specification value). However, we are willing to accept dissolution data from stability batches and other batches not tested in clinical trials which are being manufactured in the same conditions as those for the clinical batches for setting the dissolution acceptance criterion.*
   b. *The in vitro dissolution profile should encompass the timeframe over which at least (b) (4)% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.*
   c. *For immediate release product the selection of the specification time point should be where Q= (b) (4) % dissolution occurs.*

3. *The lack of the requested data and information may impact the approvability of your application. In order to review the requested data and information in this review cycle, the requested information/data needs to be submitted no later than October 30, 2013.*

Further Communications between FDA and the Applicant:

- On September 17, 2013, the Applicant submitted information regarding the dissolution method in response to the potential review issues.

- On October 31, 2013, FDA sent an Information Request (IR) to the Applicant, which recommended revising the dissolution method to include more suitable testing conditions for the drug product.

- On December 13, 2013 the Applicant submitted a revised dissolution method with supporting justification for the proposed dissolution method parameters.

- On January 31, 2014, FDA sent an IR to the Applicant, which advised them to establish dissolution acceptance criteria where Q= (b) (4)%, and told them that dissolution acceptance criteria for batch release and stability testing should be the same. The IR also requested information to account for the expected release in carbidopa monohydrate over the course of the shelf-life.

- On February 7, 2014, the Applicant submitted batch information for the experimental batches used for the dissolution method development. The dissolution data for 10 commercial-scale batches were also submitted to support the proposed dissolution acceptance criteria. Additional data also demonstrated

that carbidopa monohydrate met assay specifications ((b) (4) mg/mL) over the 15-week expiration period.

Review:
The Biopharmaceutics review is focused on the evaluation and acceptability of the proposed dissolution method and its acceptance criteria for batch release and stability testing.

RECOMMENDATION:

The following proposed dissolution method for the testing of LCIG is acceptable.

USP Apparatus	Rotation Speed	Medium	Volume	Temperature
2 (Paddle)	25 rpm	0.05 M acetate buffer, pH 4.5	500 mL	37°C

However, the dissolution data required for the setting of the dissolution acceptance criteria with the new method are very limited, and therefore critical dissolution data throughout the 15 week stability period under refrigeration conditions at 5ºC are lacking.

At this time of the review process, due to lack of critical dissolution data needed for the setting of the dissolution acceptance criteria, from the Biopharmaceutics perspective, a **COMPLETE RESPONSE (CR)** is recommended for NDA 203952 for Levodopa-Carbidopa Intestinal Gel.

The following comments and request for information should be conveyed to the Applicant in the CR letter:

1. Submit the complete dissolution profile data (*individual, mean, SD, profiles*) for each time point for the dissolution testing of the commercial-scale batches. Provide the dissolution data at the following time points: 15, 20, 30, 40, 50, and 60 minutes (n=12). The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*).

2. We acknowledge your commitment to provide stability data for your drug product under frozen (-20ºC) and refrigeration (5ºC) conditions post-approval. However, for the setting of the specifications of your drug product, you will need to provide data from at least 3 batches at the initial time point and thereafter at 5, 10, and 15 weeks under refrigeration conditions. For this testing, we consider the initial time point when the product is thawed and placed under the 5ºC refrigeration conditions. For the dissolution testing, provide the complete dissolution profile data as described in above Comment 1.

3. In your October 31, 2013 response to our Information Request (IR), you indicated [redacted (b) (4)] whereas in your February 7, 2014 IR response, you indicated that [redacted (b) (4)] a 10-fold difference. Clarify this discrepancy [redacted (b) (4)]

Signature
Kelly M. Kitchens, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Signature
Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc. SSuarez; RLostritto.

BIOPHARMACEUTICS ASSESSMENT

Drug Product:

Description: The Sinemet (levodopa-carbidopa) Tablet product is a combination of levodopa and carbidopa for the treatment of the symptoms of idiopathic Parkinson's disease (paralysis agitans). Carbidopa reduces the amount of levodopa required to produce a given response by about 75%, and increases both plasma levels and plasma half-life of levodopa. For the proposed LCIG product, continuous delivery via direct tubing to the intestine avoids the variable gastric emptying time, results in less variability in levodopa and carbidopa plasma concentrations compared to oral dosing and is believed to provide a continuous rather than intermittent stimulation of the dopaminergic receptors in the brain. LCIG also provides continuous delivery to the upper intestine, where the compounds are rapidly absorbed by an active carrier mechanism localized in the proximal small intestine.

Formulation: LCIG is a formulation of levodopa and carbidopa delivered from a medication cassette reservoir via the CADD-Legacy® 1400 portable infusion pump into the proximal small intestine through a percutaneous endoscopic gastrostomy with jejunal extension (PEG-J). The LCIG System is a drug-device combination product that includes the following elements:

a. The drug product, Levodopa-Carbidopa Intestinal Gel, 20 mg/mL or 5 mg/mL in a medication cassette reservoir; and
b. An enteral administration system, known as the LCIG Administration System. This includes: a software-driven, ambulatory infusion pump and a percutaneous endoscopic gastrostomy tube (PEG) with jejunal tube (J), plus an optional, temporary nasojejunal (NJ) tube.

The composition of LCIG is described in the following table:

Component	Quality Standard	Function	Amount per mL
Levodopa	USP	Drug Substance	20.0 mg
Carbidopa monohydrate	USP	(b) (4)	5.0 mg
Carmellose sodium [a]	USP		(b) (4)
Purified Water	USP		

(b) (4)

b. Medication Cassette Reservoir capacity is approximately 100 grams of LCIG.

Dissolution Method Development:

(b) (4)

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Reviewer's Overall Assessment of the new dissolution method: SATISFACTORY

Proposed Dissolution Acceptance Criteria

- The Applicant proposed the following acceptance criteria based on the data generated using the proposed dissolution method:

Table 7. Tentative Acceptance Criteria

Test	Limits	Time point	Q according to

- A shelf-life limit of Q= % at minutes for carbidopa monohydrate was proposed .
- Data for commercial-scale batches will be provided in an NDA amendment in the first quarter of 2014 at a suitable time as arranged with FDA. AbbVie commits to validate the dissolution method as appropriate prior to implementation.

Reviewer's comments on proposed acceptance criteria:

- *The proposed dissolution acceptance criteria are not supported by the provided dissolution data, and the acceptance criteria for batch release and stability testing should be the same.*
- *Therefore, on January 31, 2014, the following IR was communicated to the Applicant:*
    - *Submit a table including the age of the LCIG batches used for the dissolution method development (batches ABBV-1809-11, 131111-H07, 131111-H08, and 131111-H09) and the LCIG batches used for the dissolution studies (batches 131119-S01, 131119-S02, 131119-S03, 131119-S04, 131119-S05, 131119-S06). The age is the time frame between the manufacture date and the dissolution testing date.*
    - *The proposed dissolution acceptance criteria are not supported by the provided dissolution data and are not acceptable. Note that the setting of the specification time point should be where Q=(b) (4)% dissolution occurs. Therefore, using the dissolution data generated from all the tested batches with the new dissolution method, including the dissolution data you plan to submit in the NDA amendment, submit a proposal for the dissolution acceptance criteria of your product. Note that the dissolution acceptance criteria for batch release and stability testing should be the same.*
    - *Due to the degradation observed for carbidopa monohydrate, provide information to account for the expected decrease in carbidopa monohydrate release over the course of the shelf-life.*

We request this information by February 7, 2014.

APPLICANT'S RESPONSES

The Applicant submitted the following information via e-mail on February 7, 2014 in response to the IR:

Applicant's Response to request #1: The batches used for dissolution method development and dissolution studies are summarized in Table 1. These were experimental batches prepared specifically for these studies, including in most cases intentionally non-representative raw materials in order to provide a range of (b) (4) and characterize the behavior under the dissolution conditions. They were not previously frozen and generally were stored at 5°C for less than 1 week prior to use in the studies. Further description of these batches and the dissolution studies are found in the CTD provided with this response in the drug product, Justification of Dissolution Specification section (eCTD Module 3.2.P.5.6).

Table 1. Development Batch Information for Dissolution Development and Studies

Lot Number	Date of manufacture	Dissolution Profile Dates	Age (days)
ABBV-1809-11	29 Oct 13	14-15 Nov 13	16-17
131111H-07	13 Nov 13	14-15 Nov 13	1-2
131111H-08	13 Nov 13	18 Nov 13	5
131111H-09	14 Nov 13	19 Nov 13	5
131119S-01	19 Nov 13	20 Nov 13	1
131119S-01	19 Nov-13	22 Nov 13	3
131119S-02	22 Nov 13	25 Nov 13	3
131119S-03	22 Nov 13	25 Nov 13	3
131119S-04	22 Nov 13	25 Nov 13	3
131119S-05	22 Nov 13	26 Nov 13	4

Reviewer's comments to request #1 response:

- *With the exception of batch ABBV-1809-11, the experimental batches were of similar age range. The batch information was not provided for batch 131119-S06. However, the Applicant conducted additional dissolution testing on commercial-scale batches to establish dissolution acceptance criteria for levodopa and carbidopa monohydrate. Therefore, the missing data for batch 131119-S06 will not be requested.*
- *The Applicant's response is acceptable.*

Applicant's Response to request #2: The following are specification criteria (being amended to the NDA as part of this response) for dissolution testing of Levodopa-Carbidopa Intestinal Gel (LCIG) using USP Apparatus 2 at 25 rpm with 500 mL of 0.05 M acetate buffer, pH 4.5, maintained at 37°C:

Specification
Levodopa: Q = (b) (4)% at 40 minutes
Carbidopa monohydrate: Q = (b) (4)% at 40 minutes

Acceptance criteria will be applied per the Acceptance Table in USP General Chapter <711>. These criteria are based upon the dissolution test results from all the tested batches utilizing Dissolution Test Procedure RTM.C5531, being submitted to the NDA in eCTD Module 3.2.P.5.2. These test results from experimental and commercial scale batches are included in the NDA amendment in the drug product, Justification of Dissolution Specification section (eCTD Module 3.2.P.5.6). The Module 3 documents that are new or updated to reflect the revised dissolution criteria are summarized in Table 2. No other changes were made to the affected module 3 documents.

Reviewer's comments to request #2 response:

- Dissolution testing was conducted using the proposed dissolution method on the following batches (all within (b) (4) specifications) to establish dissolution acceptance criteria for levodopa and carbidopa monohydrate:

Table 1. Batch Information for LCIG Commercial-Scale Batches Evaluated in the Dissolution Assessment

Lot Number	Clinical Trial	Date of Manufacture	Drug Substance Manufacturer	(b) (4)
12D11G07	Not applicable	11 Apr 2012		
12H09G07	M12-920	09 Aug 2012		
12J18G15	M12-920	12 Oct 2012		
13D11G13	S187.3.005	11 Apr 2013		
13D18G21	S187.3.005	18 Apr 2013		
13E10G08	Not applicable	10 May 2013		
13F13G15	S187.3.005	13 Jun 2013		
13F20G23	S187.3.005	20 Jun 2013		
13H20G20	Not applicable	20 Aug 2013		
13J16G15	Not applicable	16 Oct 2013		

- The following dissolution data were provided for these batches:

Table 2. Detail of Dissolution at 40 Minutes, Ten Commercial-Scale Batches

Lot Number	Levodopa (% Label Claim)			Carbidopa Monohydrate (% Label Claim)		
	Mean	Lowest Individual	Highest Individual	Mean	Lowest Individual	Highest Individual
12D11G07						
12H09G07						
12J18G15						
13D11G13						
13D18G21						
13E10G08						
13F13G15						
13F20G23						
13H20G20						
13J16G15						

(b) (4)

(b) (4)

Figure 4. Dissolution of Levodopa: LCIG Commercial-Scale Batches

Figure 5. Dissolution of Carbidopa Monohydrate: LCIG Commercial-Scale Batches

- The dissolution data are incomplete since only the dissolution values at the 40 minutes time point were submitted. Complete multipoint dissolution profile data from the dissolution testing is needed for the setting of the dissolution acceptance criteria. Therefore, there are very limited data to make a recommendation and at

this time FDA does not concur with the Applicant's proposed acceptance criteria. The Applicant will be requested to submit the complete dissolution profile data for the dissolution testing of the commercial-scale batches.

Applicant's Response to request #3 (summarized by the Reviewer):
The finished drug product is distributed by AbbVie to the pharmacy in the frozen state. Prior to shipping to the patient, the pharmacy thaws the frozen cassettes, adds a (b) (4) week expiration date, and medication cassette reservoirs are stored in a refrigerator until the day of use. (b) (4) Over (b) (4) weeks, the expected decline in carbidopa monohydrate content is a mean value of (b) (4)%. The (b) (4) week expiration period provides high confidence that the carbidopa concentration of a batch is within assay specifications ((b) (4) mg/mL) up through the labeled expiry date. For the convenience of the reviewer, the results of the calculations from the Carbidopa Monohydrate Assay section, found in eCTD Module 3.2.P.8.1, are also provided here in Table 3 and Figure 1.

Table 3. Carbidopa Monohydrate Assay Summary for Levodopa-Carbidopa Intestinal Gel, 20 mg/mL-5 mg/mL, in Medication Cassette Reservoirs at 2 to 8°C (CSSI model)

	Lot 10C14G10	Lot 10C15G11	Lot10C16G12
Slope, mg/mL per week	(b) (4)		
Intercept, mg/mL			
Shelf life, weeks, 95% confidence			
Mean prediction at (b) (4) mg/mL			
Lower limit at (b) (4) 95% confidence, mg/mL			
Upper limit at (b) (4) 95% confidence, mg/mL			

Figure 1. Predicted and Actual Results for Carbidopa Monohydrate Assay in Levodopa-Carbidopa Intestinal Gel, 20 mg/mL 5 mg/mL, in Medication Cassette Reservoirs at 2 to 8°C

Impact on Dissolution Test Results

While the rate of dissolution of carbidopa monohydrate remains stable over the course of the refrigerated shelf-life, any stability result reported as % of labeled amount will reflect a time-based decrease in carbidopa monohydrate concentration in the suspension as a result of degradation over the course of the stability study. The dissolution profile is related to the potency, therefore when degradation occurs, the profile will be shifted lower for the carbidopa monohydrate. Note that the pH of the dissolution medium is chosen so that degradation is not a factor during the period of the dissolution analysis itself. The method validation shows stability up to 2 days for the timed dissolution samples.

Reviewer's comments to request #3 response:

- In the October 31, 2013 IR response, the Applicant indicated that (b) (4) whereas in the February 7, 2014 IR response, the Applicant indicated that (b) (4) a 10-fold difference. The Applicant will be requested to clarify this discrepancy (b) (4) .
- The submitted carbidopa monohydrate data show that carbidopa monohydrate concentrations are within assay specifications during the (b) (4) week expiration period. This indicates that dissolution acceptance criteria for carbidopa monohydrate batch release and stability testing should be the same.

- The Applicant committed to continue the stability studies on the primary stability batches at the long-term storage condition.
- The following dissolution method validation is acceptable:

Validation Attribute	Acceptance Criteria	Results Summary
[redacted]	[redacted]	[redacted] (b) (4)

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RECOMMENDATION:

The new proposed dissolution method for LCIG is acceptable. However, the dissolution data required for the setting of the dissolution acceptance criteria with the new method are very limited, and therefore critical dissolution data throughout the 15 week stability period under refrigeration conditions at 5ºC are lacking.

At this time of the review process, due to lack of critical dissolution data needed for the setting of the dissolution acceptance criteria, from the Biopharmaceutics perspective, a **COMPLETE RESPONSE (CR)** is recommended for NDA 203952 for Levodopa-Carbidopa Intestinal Gel.

The following comments and request for information should be conveyed to the Applicant in the CR letter:

1. Submit the complete dissolution profile data (*individual, mean, SD, profiles*) for each time point for the dissolution testing of the commercial-scale batches. Provide the dissolution data at the following time points: 15, 20, 30, 40, 50, and 60 minutes (n=12). The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*).

2. We acknowledge your commitment to provide stability data for your drug product under frozen (-20ºC) and refrigeration (5ºC) conditions post-approval. However, for the setting of the specifications of your drug product, you will need to provide data from at least 3 batches at the initial time point and thereafter at 5, 10, and 15 weeks under refrigeration conditions. For this testing, we consider the initial time point when the product is thawed and placed under the 5ºC refrigeration conditions. For the dissolution testing, provide the complete dissolution profile data as described in above Comment 1.

3. In your October 31, 2013 response to our Information Request (IR), you indicated that (b) (4) ; whereas in your February 7, 2014 IR response, you indicated that (b) (4) a 10-fold difference. Clarify this discrepancy (b) (4)

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/s/

KELLY M KITCHENS
02/21/2014

ANGELICA DORANTES
02/21/2014